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Randomized, Double-Blind, Multicenter Study of the Endeavor Zotarolimus-Eluting Phosphorylcholine-Encapsulated Stent for Treatment of Native Coronary Artery Lesions

Clinical and Angiographic Results of the ENDEAVOR II Trial

Jean Fajadet, MD; William Wijns, MD, PhD; Gert-Jan Laarman, MD; Karl-Heinz Kuck, MD; John Ormiston, MD; Thomas Münzel, MD, PhD; Jeffrey J. Popma, MD; Peter J. Fitzgerald, MD; Raoul Bonan, MD; Richard E. Kuntz, MD, MSc; for the ENDEAVOR II Investigators

Background—The use of the Endeavor stent might reduce restenosis and stent thrombosis at 9 months.

Methods and Results—Patients (n=1197) treated for single coronary artery stenosis were enrolled in a prospective, randomized, double-blind study and randomly assigned to receive the Endeavor zotarolimus-eluting phosphorylcholine polymer–coated stent (n=598) or the same bare metal stent but without the drug or the polymer coating (n=599). The 2 groups were well matched in baseline characteristics. Diabetes was present in 20.1% of patients; the mean reference vessel diameter was 2.75 mm; and the mean lesion length was 14.2 mm. The primary end point of target vessel failure at 9 months was reduced from 15.1% with the bare metal stent to 7.9% with the Endeavor (P=0.0001), and the rate of major adverse cardiac events was reduced from 14.4% with the bare metal stent to 7.3% with the Endeavor (P=0.0001). Target lesion revascularization was 4.6% with Endeavor compared with 11.8% with the bare metal stent (P=0.0001). The rate of stent thrombosis was 0.5% with the Endeavor, which was not significantly different from 1.2% with the bare metal stent. In 531 patients submitted to angiographic follow-up, late loss was reduced from 1.03±0.58 to 0.61±0.46 (P<0.001) in stent and from 0.72±0.61 to 0.36±0.46 (P<0.001) in segment. The rate of in-segment restenosis was reduced from 35.0% to 13.2% with Endeavor (P<0.0001). There was no excessive edge stenosis, aneurysm formation, or late acquired malapposition by intravascular ultrasound imaging. Differences in clinical outcome were maintained at 12 and 24 months (P<0.0001).

Conclusions—Compared with bare metal stents, the Endeavor stent is safe and reduces the rates of clinical and angiographic restenosis at 9, 12, and 24 months. (***Circulation.* 2006;114:798-806.**)

Key Words: coronary disease ■ restenosis ■ revascularization ■ stents

Endoluminal metallic stents became the default treatment for percutaneous coronary interventions after clinical trials indicated that stenting decreased reintervention rates compared with balloon angioplasty.[1–3] With the use of bare metal stents, clinical and angiographic restenosis still occurs in a large number of patients, with rates as high as 20% to 40% in high-risk subgroups.[4–6] The principal cause of in-stent restenosis is neointimal hyperplasia resulting from proliferation and migration of smooth muscle cells and extracellular matrix production.[7] Stents coated with antiproliferative agents have successfully addressed these problems.

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Indeed, polymer-based local delivery of sirolimus or paclitaxel from eluting stent platforms has drastically reduced restenosis rates.[8–10] However, the antiproliferative properties of currently available drug-eluting stents prevent or delay vessel healing.[11,12] Delayed healing and polymer degradation have been associated with stent malapposition, hypersensitivity reactions, and most important, late stent thrombosis.[13–15] Concerns[16,17] about mid- and long-term safety of drug-eluting stents have stimulated the development of new drug-eluting

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The study investigators and participating institutions are listed in the Appendix, which is available in the online-only Data Supplement at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.591206/DC1.

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stents with equivalent antirestenosis capabilities but improved safety profile, one of which is the Endeavor zotarolimus-eluting stent. The potential for the zotarolimus-eluting stent to reduce target lesion revascularization (TLR) to 1% at 1 year has been demonstrated in a first-in-human study.[18] The present study is a large-scale, prospective, randomized, double-blind, multicenter trial designed to examine the safety and efficacy of the Endeavor stent in reducing the risk of clinical and angiographic restenosis in patients/lesions with moderate restenosis risk compared with the same bare stent without the phosphorylcholine polymer or antiproliferative drug.

Methods

Patients and Protocol

Patients with clinical evidence of ischemia or a positive function study who were undergoing stenting of a single, previously untreated lesion in a native coronary were considered for enrollment. Major exclusion criteria were left ventricular ejection fraction <30%; significant (>50%) stenosis proximal or distal to the target lesion; myocardial infarction (MI) within the preceding 72 hours; contraindications or allergy to aspirin, heparin, clopidogrel, cobalt, nickel, or chromium; hypersensitivity to contrast media; serum creatinine level >2.0 mg/dL (177 μmol/L); leukocyte count <3000 cells/mm^3 or platelet count <100 000 or >700 000 cells/mm^3; current participation in other investigational trials; or any coronary interventional procedure within 30 days before or planned after the implantation of the study stent. Angiographic inclusion criteria were a reference vessel diameter of 2.25 to 3.50 mm and a lesion length >14 but ≤27 mm, as estimated by the investigator. Angiographic exclusion criteria included left main or ostial target lesion, severe calcification by angiography, bifurcation lesion, and location of the target lesion at a >45° bend. The study was conducted according to the Declaration of Helsinki. The medical ethics committees of all sites approved the study protocol, and written informed consent was obtained from every patient.

Stent System

The Driver bare metal stent (Medtronic, Santa Rosa, Calif) received European CE Marking in November 2002 and approval from the US Food and Drug Administration in October 2003 for the treatment of coronary lesions. This cobalt-alloy stent has a low profile, with a strut thickness of 0.0036 in (91 μm), designed to improve tracking and crossing in tortuous anatomy. A prospective multicenter registry study of 297 patients confirmed the good performance of the Driver stent.[19] The Endeavor stent system (Medtronic) consists of the same bare metal stent coated with phosphorylcholine, from which 10 μg zotarolimus per 1 mm stent length is eluted. The polymer phosphorylcholine coating is a synthetic copy of the predominant phospholipid in the outer membrane of red blood cells and shows high biovascular compatibility. In animal studies, phosphorylcholine-coated stents have demonstrated significantly less platelet adhesion compared with uncoated stents.[20] A phosphorylcholine coating also was used by the BiodivYsio stent (Biocompatibles Ltd, Farnham, UK) and was found safe and effective in the Study of Phosphorylcholine Coating on Stents (SOPHOS) trial.[21] Sirolimus and its analogs, including zotarolimus, block activation of the mammalian target of rapamycin. This blockage keeps smooth muscle cells from advancing from the G1 phase of cell cycle activity into DNA synthesis and cell division.[22,23] The drug and polymer are asymmetrically distributed on the stent surface by a proprietary coating technique, so the drug is localized mainly on the ablumenal arterial wall side of the stent.[24]

Randomization and Stent Implantation

Randomization was performed by an interactive telephone system. Patients were assigned (1:1) to treatment with either the Endeavor zotarolimus-eluting stent or the visually indistinguishable Driver bare metal stent without drug and polymer.

Seventy-two sites in Europe, Asia Pacific, Israel, New Zealand, and Australia participated in this study. Stents were implanted according to a standardized procedure. Before catheterization, patients received a minimum of 75 mg aspirin and a 300-mg loading dose of clopidogrel; a baseline ECG was obtained; and creatinine kinase and isoenzyme levels were measured. Unfractionated heparin was administered to maintain activated clotting time >250 seconds or between 200 and 250 seconds if a glycoprotein IIb/IIIa inhibitor was administered at the operator's discretion. Predilatation was mandatory. The predilatation balloon could be no longer than the stent intended for implantation, and selecting a stent long enough to completely cover the diseased vessel segment was recommended. Stents were available in lengths of 18, 24, and 30 mm and sizes of 2.25, 2.50, 3.00, and 3.50 mm. In the event of edge dissection or incomplete coverage, additional stents could be implanted at the operator's discretion up to a maximum length of 48 mm. Postdilatation could be performed within the deployed stent as required to optimize stent expansion. After the procedure, an ECG was obtained, and cardiac enzymes were measured. Patients took aspirin daily indefinitely (at least 75 mg daily), and clopidogrel was prescribed for 12 weeks (75 mg daily). Clinical follow-up was scheduled for 30 days, 6 months, 9 months, and yearly thereafter for 5 years. In addition, the first 600 patients enrolled were scheduled to undergo angiographic follow-up at 8 months, among whom 300 patients were scheduled to undergo intravascular ultrasound after the procedure and at 8 months.

Data Management

The study was monitored by an independent contract research organization (Quintiles Transnational, Research Triangle Park, NC), and the trial and data were coordinated and analyzed by the Harvard Clinical Research Institute (Boston, Mass). All major adverse cardiac events (MACE) were reviewed and adjudicated by an independent clinical events committee, whose members were unaware of treatment allocation. An independent data and safety monitoring board periodically reviewed blinded safety data.

End Points and Definitions

The primary end point was the 9-month rate of target vessel failure (TVF), defined as a composite of target vessel revascularization (TVR), recurrent Q-wave or non–Q-wave MI, or cardiac death that cannot be clearly attributed to a vessel other than the target vessel. TLR was defined as repeat revascularization for ischemia owing to stenosis ≥50% of the lumen diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent. Revascularization of ≥70% stenosis in the absence of ischemic signs or symptoms also was considered clinically driven. MI was defined either as the development of pathological Q waves in at least 2 contiguous leads with or without elevated cardiac enzymes or, in the absence of pathological Q waves, as an elevation in creatinine kinase levels to greater than twice the upper limit of normal in the presence of an elevated creatinine kinase-MB level. Enzyme levels were available in 581 of 592 Endeavor recipients and in 577 of 591 patients in the bare metal stent group.

Secondary end points were MACE, defined as death, MI (Q-wave and non–Q-wave MI), emergent cardiac bypass surgery, or TLR (repeat percutaneous transluminal coronary angioplasty or coronary artery bypass grafting); angiographic late loss; and binary restenosis, defined as stenosis of ≥50% of the lumen diameter of the treated lesion. Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of vessel occlusion or thrombus within or adjacent to a previously stented segment; in the absence of angiography, stent thrombosis could be confirmed by acute MI in the distribution of the treated vessel or death resulting from cardiac causes within 30 days.

Angiographic Analysis

Image acquisition was performed with ≥2 angiographic projections, intracoronary nitroglycerin to provide maximum coronary vasodila-

tion, and repetition of identical angiographic projections at follow-up angiography. Cineangiograms were then forwarded to the Brigham and Women's Hospital Angiographic Core Laboratory in Boston, Mass, for standardized review by observers blinded to treatment assignment. Lesion length was defined as the axial extent of the lesion that contained a shoulder-to-shoulder lumen reduction by ≥20%. Restenosis patterns were qualitatively assessed with the Mehran classification system.[25] Coronary aneurysms were defined as a maximum lumen diameter within the treatment zone that was 1.2 times larger than the average reference diameter of the vessel. Using the contrast-filled injection catheter for calibration, we performed quantitative angiographic analysis with a validated automated edge detection algorithm (Medis CMS, Leiden, the Netherlands)[26] on selected images demonstrating the stenosis in its "sharpest and tightest" view. A 5-mm segment of reference diameter proximal and distal to the stenosis was used to calculate the average reference vessel diameter; side branches and other anatomic landmarks were used to identify and maintain the consistency of the analysis. Angiographic measurements were reported separately for the vessel section within the stent ("in stent"), for the vessel portions extending 5 mm from the proximal and distal stent edges, and for the entire segment ("in segment"). Total occlusions were assigned a minimum lumen diameter of 0 mm and a 100% diameter stenosis. Late loss was defined as the difference between minimum lumen diameter after the procedure and at 8 months. Loss index was determined by dividing late loss by short-term gain.

Statistical Analysis

The statistical analysis plan prespecified that the primary intention-to-treat population would consist of all patients in whom an attempt was made to implant a study stent. For the primary end point of TVF, we projected a 40% reduction at 9 months from an anticipated 16% with bare metal stenting to 9.5% with the Endeavor stent. Using a 2-sided test for differences in independent binomial proportions with an α level of 0.05 and assuming an 8% loss to clinical follow-up, we calculated that 1200 patients would have to undergo randomization to detect this relative reduction with 90% power. For the secondary end point of angiographic late loss, we assumed that the mean difference in in-stent late loss at 8 months would be >0.21 mm between the 2 arms using a standard deviation of 0.70 mm. A sample size of 600 subjects was needed for the 2-sided test for differences of the secondary end point of late loss, using an α level of 0.05 and a power of 90% and assuming a 20% loss to angiographic follow-up.

Categorical discrete variables were compared by the χ^2 test or the Fisher exact test when appropriate. Continuous variables are presented as mean±SD and were compared with the use of the Student t test or the Wilcoxon 2-sample test for nonnormally distributed data. The interactions between 3 categorical variables (diabetes mellitus, vessel size, and lesion length) and treatment assignment were tested by logistic regression. All probability values are 2 sided.

The authors had full access to the data and take responsibility for their integrity. All authors have read and agree to the manuscript as written.

TABLE 1. Baseline Clinical and Lesion Characteristics*

Characteristic	Endeavor Stent (n=598)	Bare Metal Stent (n=599)
Age, y	61.6±10.5	61.9±10.5
Male sex, %	77	75
Prior MI, %	40	42
Prior percutaneous coronary intervention, %	22	18
Diabetes mellitus, %	18	22
Unstable angina, %	30	30
Hyperlipidemia requiring treatment, %	81	77
Current smoking, %	35	35
Target lesion coronary artery, %		
Left anterior descending	43	48
Left circumflex	22	21
Right	34	31
Reference vessel diameter, mm	2.74±0.48	2.76±0.49
Lesion length, mm	14.05±5.57	14.38±5.73
Minimum lumen diameter, mm	0.83±0.34	0.84±0.35
Stenosis, %	69.7±10.8	69.5±11.0
Type B1/B2 lesion, %	69	72
Type C lesion, %	28	24

*Values are mean±SD when appropriate. There were no significant differences between groups.

TABLE 2. Stent Implantation and Procedural Results*

Variable	Endeavor Stent (n=598)	Bare Metal Stent (n=599)
Lesion success, %†	99.8	100.0
Device success, %‡	98.8	99.2
Procedure success, %§	96.4	96.4
Stent diameter, mm	3.08	3.08
Stent length, mm	23.4	23.4
Stent-to-lesion length ratio	1.84	1.80
Stents per lesion, n	1.13	1.12
Overlapping stents, %	9.0	8.2
Use of glycoprotein IIb/IIIa inhibitors, %	13.2	10.4
Final reference vessel diameter, mm	2.78±0.47	2.80±0.50
Final minimum lumen diameter, mm		
In stent	2.59±0.43	2.61±0.44
In segment	2.21±0.49	2.24±0.49
Final stenosis, % lumen diameter		
In stent	6.06±10.44	6.22±10.04
In segment	20.55±10.77	20.21±9.55
Acute gain, mm		
In stent	1.76±0.44	1.77±0.44
In segment	1.38±0.47	1.40±0.47

*Values are mean±SD when appropriate. There were no significant differences between groups.

†Lesion success was defined as <50% residual in-stent final stenosis.

‡Device success was defined as <50% residual in-stent final stenosis with assigned stent.

§Procedure success was device success and no in-hospital MACE.

Results

Baseline Characteristics and Procedural Results

Between July 14, 2003, and January 13, 2004, 1197 patients were assigned to receive either the Endeavor zotarolimus-eluting stent (598 patients) or a bare metal stent (599 patients). The baseline characteristics of the 2 groups were well matched (Table 1). The lesion, procedure, and device-deployment success rates approached 100% in the 2 groups; procedural variables and initial angiographic results were similar for the 2 groups (Table 2 and Figure 1).

Clinical Outcomes

Clinical follow-up at 9 months was completed for 1183 of 1197 patients (98.8%). Compared with the bare metal stent,

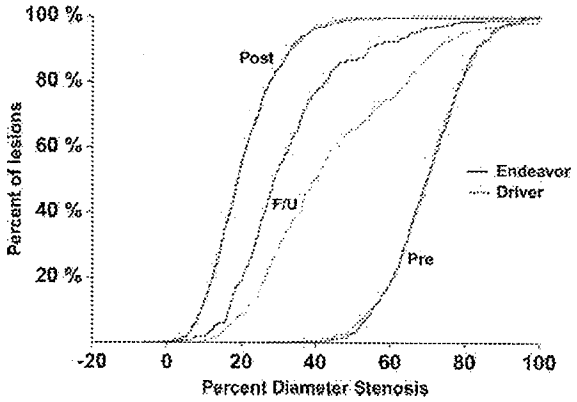

Figure 1. Cumulative frequency distribution for in-segment diameter stenosis (percent of lumen diameter) for the Endeavor and bare metal stents before and immediately after intervention and at 8 months. The curves are superimposed before (Pre) and after the procedure. At the 8-month follow-up (F/U), the distribution curve for Endeavor (solid line) is shifted left (lower percent diameter stenosis values).

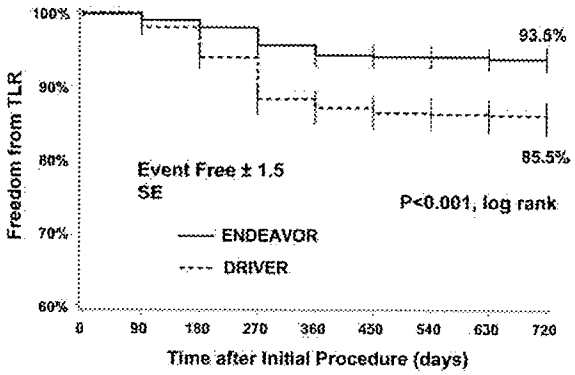

Figure 2. Freedom from TLR in both groups. The curves start to diverge after 3 months; statistical difference is reached at 4 months and increases over time up to 9 months. The absolute risk reduction is 7.6% (95.4% to 87.8%) at 9 months. Differences in outcome are maintained at 24 months ($P<0.0001$). Of note, freedom from TLR is high in both groups.

implantation of the zotarolimus-eluting stent reduced the primary end point of TVF at 9 months by 47.7% and lowered TLR by 61.0% (Table 3). There was no significant difference between site-reported and adjudicated ischemia-driven revascularization. TLR rates for Endeavor were 3.9% by site and 4.6% by adjudication. TLR rates for bare metal stent were 9.8% by site and 11.8% by adjudication. The rates of death, MI, and stent thrombosis were low and similar in the 2 groups. At the 9-month follow-up, the TVR and MACE rates were significantly lower with the Endeavor stent compared with the bare metal stent (Table 3 and Figure 2). Stent thrombosis was very low in each group (0.5% for the zotarolimus-eluting stent, 1.2% for the bare metal stent). In the Endeavor group, no documented stent thrombosis was observed beyond 30 days up to 24 months after implantation. Clinical follow-up is available for 1179 patients (98.5%) and 1160 patients (96.9%) at 12 and 24 months, respectively. By 12 months, MACE rates remained significantly lower for the zotarolimus-eluting stent (8.8% versus 15.6%; $P=0.0004$), and TLR occurred in 5.9% compared with 13.1% ($P<0.0001$). By 24 months, MACE rates were 10.0% versus 18.7% ($P<0.0001$), and TLR was 6.5% versus 14.7%

TABLE 3. Clinical Outcomes at 270 Days

Outcome	Endeavor Stent (n=592)	Bare Metal Stent (n=591)	Relative Risk (95% CI)	*P*
TVF, %*	7.9	15.1	0.53 (0.38–0.74)	0.0001
MACE, %†	7.3	14.4	0.51 (0.36–0.72)	0.0001
Death, %	1.2	0.5	2.33 (0.61–8.96)	0.342
Cardiac/noncardiac death, n	5/2	3/0	...	...
MI, %	2.7	3.9	0.69 (0.37–1.30)	0.260
Q wave	0.3	0.9	0.40 (0.08–2.05)	0.287
Non–Q wave	2.4	3.1	0.78 (0.39–1.55)	0.481
Emergent CABG, %	0.0	0.0	...	...
TLR, %	4.6	11.8	0.39 (0.25–0.59)	0.0001
CABG, %	0.3	0.5	0.67 (0.11–3.97)	0.687
Percutaneous coronary intervention, %	4.2	11.3	0.37 (0.24–0.58)	<0.0001
TVR, %	5.6	12.5	0.45 (0.30–0.66)	<0.0001
Stent thrombosis	0.5	1.2	0.43 (0.11–1.65)	0.224
In hospital	0.3	0.3	1.00 (0.14–7.06)	1.00
Up to 30 d after discharge	0.3	0.8	0.40 (0.08–2.05)	0.287
>30 to 270 d, %	0.0	0.0	...	...

CABG indicates coronary artery bypass grafting.

*TVF was defined as TVR, recurrent Q-wave or non–Q-wave MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel.

†MACE was defined as death, MI, emergent cardiac bypass surgery, or TLR (repeat percutaneous transluminal coronary angioplasty or coronary artery bypass grafting).

TABLE 4. Impact of Systematic Repeat Angiography on Clinically Driven TLR and TVR Rates

Population	Endeavor Stent	Bare Metal Stent	*P*
Total, n	592	591	
TLR, %	4.6	11.8	<0.0001
TVR, %	5.6	12.5	<0.0001
Angiography subset, n	295	297	
TLR, %	5.8	15.8	<0.0001
TVR, %	6.8	16.8	0.0002
Nonangiography subset, n	297	294	
TLR, %	3.4	7.8	0.020
TVR, %	4.4	8.2	0.063

Per protocol, half of the patients were assigned to undergo invasive follow-up (angiography subset).

($P<0.0001$) for the Endeavor versus the bare metal stent, respectively.

Angiographic and Intravascular Ultrasound Imaging Results

Angiography at 8 months was completed for 531 of the prespecified patients (88.5%). There was no significant difference in baseline characteristics, angiographic parameters, or procedural data between patients assigned to angiographic or clinical follow-up. In the angiographic cohort, average lesion length was 13.29 mm in patients assigned to Endeavor compared with 14.15 mm in patients receiving the bare metal stent ($P=0.05$).

In patients assigned to invasive follow-up, TLR rates were higher for both groups (15.8% and 5.8% for the bare metal and Endeavor stents, respectively) than for patients assigned to clinical follow-up (7.8% and 3.4% for the bare metal and Endeavor stents, respectively). Likewise, TVR rates were higher for both groups assigned to undergo systematic repeat angiography (Table 4).

Compared with the bare metal stent, patients who received the Endeavor stent had a significantly smaller late loss and a lower loss index. As a result, their mean minimum lumen diameters were greater, and they had a smaller mean degree of stenosis in stent, at both proximal and distal edges, and in segment (Table 5 and Figure 1). The use of an Endeavor stent reduced the risk of in-stent binary restenosis by 71.9% and in-segment binary restenosis by 62.3%. By intravascular ultrasound at 8 months for 132 patients who received the zotarolimus-eluting stent and 118 who received the bare metal stent, there was no late-acquired stent malapposition or coronary aneurysm. Evenly distributed coverage of the Endeavor stents by neointimal hyperplasia was observed.

As for the rates of clinical end points according to prespecified subgroups, treatment effect was similar across

TABLE 5. Angiographic Measures at 8 Months*

Variable	Endeavor Stent (n=265)	Bare Metal Stent (n=266)	*P*
Reference vessel diameter, mm	2.75±0.43	2.78±0.48	0.404
Minimum lumen diameter, mm			
In stent	1.99±0.56	1.62±0.70	<0.0001
In segment	1.86±0.55	1.56±0.67	<0.0001
Proximal edge	2.53±0.62	2.49±0.71	0.539
Distal edge	2.28±0.54	2.18±0.60	0.056
Diameter stenosis, % of lumen diameter			
In stent	27.9±17.3	42.3±21.7	<0.0001
In segment	32.6±16.3	44.4±20.4	<0.0001
Proximal edge	8.3±17.3	10.7±19.9	0.143
Distal edge	17.7±13.8	22.1±16.1	0.0008
Binary restenosis, %†			
In stent	9.4	33.5	<0.0001
In segment	13.2	35.0	<0.0001
Proximal edge	3.5	4.3	0.656
Distal edge	1.9	5.3	0.059
Late loss, mm			
In stent	0.61±0.46	1.03±0.58	<0.001
In segment	0.36±0.46	0.72±0.61	<0.001
Proximal edge	0.21±0.45	0.30±0.54	0.044
Distal edge	0.05±0.38	0.22±0.46	<0.001
Loss index, mm			
In stent	0.35±0.27	0.59±0.37	<0.001
In segment	0.24±0.38	0.51±0.50	<0.001

*Values are mean±SD when appropriate.
†Binary restenosis was defined as >50% diameter stenosis.

TABLE 6. Subgroup Analysis for the Rate of In-Stent Binary Angiographic Restenosis Among Patients Who Underwent Angiographic Follow-Up at 8 Months and Initially Were Assigned to Receive Either the Endeavor Zotarolimus-Eluting Stent or the Bare Metal Stent

Group	Patients, n	Endeavor Stent, %	Bare Metal Stent, %	Relative Risk (95% CI)	P
All	531	9.4	33.5	0.28 (0.19–0.42)	<0.0001
Diabetes	...	...	...	...	0.78*
No	423	7.8	30.7	0.25 (0.15–0.42)	<0.0001
Not insulin dependent	77	16.7	41.5	0.40 (0.18–0.91)	0.02
Insulin dependent	29	20.0	47.4	0.42 (0.11–1.59)	0.25
Reference vessel diameter, mm	...	...	...	...	0.24*
<2.5 mm	171	18.2	38.6	0.47 (0.28–0.79)	0.0037
≥2.5 to <3.0	205	4.6	35.1	0.13 (0.05–0.32)	<0.0001
≥3.0	152	6.0	27.1	0.22 (0.08–0.61)	0.0006
Lesion length, mm	...	...	...	...	0.20*
<11.1	179	10.6	18.8	0.57 (0.27–1.18)	0.14
≥11.1 to <16.0	194	7.4	36.4	0.20 (0.09–0.43)	<0.0001
≥16.0	149	11.4	46.8	0.24 (0.12–0.49)	<0.0001

*This probability value refers to the interaction term between treatment and subgroup effect. Nonsignificant probability value indicates that a similar treatment effect is present across all subsets.

patient/lesion subsets, as indicated by the nonsignificant interaction term of the subgroup category and treatment assignment (Table 6 and Figure 3). In patients with non–insulin-dependent diabetes (n=168), TLR rates were reduced from 15.9% with the Driver to 6.3% with the zotarolimus-eluting stent (P=0.054). In patients with insulin-dependent diabetes (n=70), TLR rates were 13.6% and 11.5%, respectively (P=1.00). In patients assigned to invasive follow-up, the relative reduction in binary angiographic restenosis with the Endeavor stent was independent of diabetes mellitus status, the diameter of the reference vessel, and lesion length (Table 6).

Discussion

Summary of Findings

In this prospective, randomized, double-blind, multicenter study of patients with previously untreated coronary lesions, implantation of the zotarolimus-eluting stent reduced the risk of angiographic restenosis at 8 months by 71.9% compared with a bare metal stent. The clinical efficacy and safety of the Endeavor stent were evidenced by a 47.7% relative reduction in TVF, a 61.0% reduction in TLR, and a 49.3% reduction in overall MACE at 9 months. Superior outcome was maintained at 2 years, and stent thrombosis was infrequent in both groups, with no documented late stent thrombosis. The rates of death from cardiac causes, including MI, also were low and were not significantly different between the 2 groups. No aneurysms were reported for any of the patients, and no late acquired stent malapposition was observed. Use of a biomimetic polymer as the drug-releasing platform might have contributed to the safety of this device.

Trial Design

Despite the large number of participating sites scattered over 4 continents, trial execution was carefully monitored, and quality of the data was ensured, as reflected in the high rates of clinical and angiographic follow-up. Systematic repeat angiography was restricted to half of the patient population. In this way, non–clinically driven redilatations are limited and the rates of repeat intervention are more likely to reflect real-life practice.[27] Indeed, systematic repeat angiography resulted in an increase in TLR and TVR rates in both subgroups, reminiscent of previous observations.[27] During the time period of patient enrollment, drug-eluting stents were not yet universally available at the participating sites, so randomization against a bare metal stent was still possible and ethically justifiable. Of note, the clinical outcome in patients randomized to bare metal stenting is satisfactory and was either superior[8] or equivalent[9] to the results obtained in the control arms of other pivotal drug-eluting stent trials.

Comparison With Other Drug-Eluting Stents

This randomized trial was powered for both the angiographic and the clinical end point.

Although neointimal hyperplasia was significantly reduced with the Endeavor stent, neointimal proliferation was not abolished as reported for other drug-eluting stents.[28] A mathematical model describing the relation between in-stent late loss and binary angiographic restenosis was recently proposed by Mauri et al.[29] Incremental steps in binary angiographic restenosis occur as in-stent late loss increases. When late loss increases from 0.2 to 0.4 mm, restenosis is predicted to increase by 3.1%, and when late loss increases from 0.4 to 0.6 mm, restenosis is expected to increase by 6.4%. The results observed in the present trial concur with that mathematical model. Along with the increasing values of late loss from SIRIUS (0.17 mm) to TAXUS IV (0.39 mm) to ENDEAVOR II (0.61 mm), observed restenosis rates were 3.2%, 5.5%, and 9.4%, respectively. However, establishing a new drug-eluting stent requires a large pivotal trial (>1000 to 2000 subjects) evaluating clinical end points. When these results are compared with either SIRIUS or TAXUS IV, all

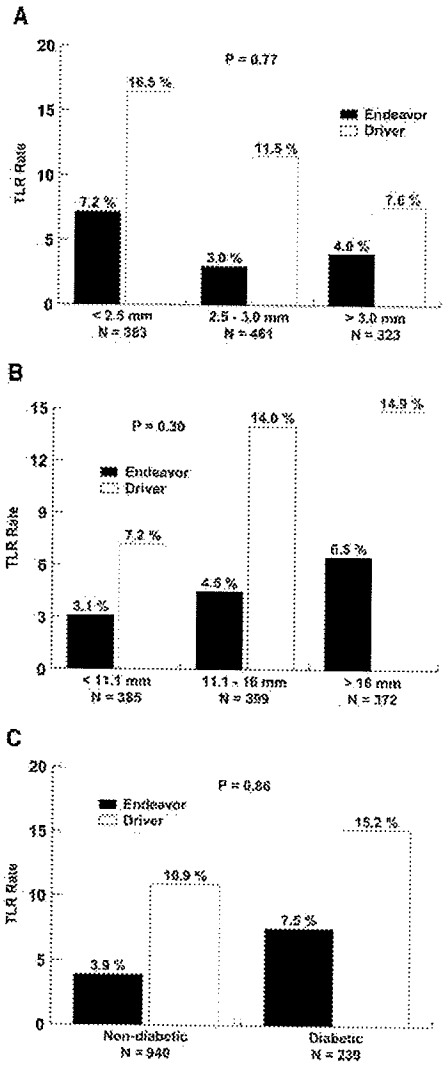

Figure 3. Impact of subset analysis on TLR rates. A, Tertiles of vessel size. After the use of a bare metal stent, TLR rate increases as vessel size decreases. With the zotarolimus-eluting stent, the treatment effect is uniform across vessels sizes. B, Tertiles of lesion length. After the use of a bare metal stent, TLR rate increases as lesion length increases. With the zotarolimus-eluting stent, the treatment effect is uniform across different lesion lengths. C, TLR rates by diabetes and treatment. TLR rates are higher in patients with diabetes in both arms. However, a uniform treatment effect is observed.

metrics of clinical outcome show nearly identical single-digit figures.[8,9] For instance, TVF rates were 8.6%, 7.6%, and 7.9% for SIRIUS, TAXUS IV, and ENDEAVOR II, respectively. This observation confirms the disconnect between clinical outcome and angiographic measures that was already noted in the ENDEAVOR I trial.[18] It also raises important questions about the value of angiographic surrogate end points as predictors of clinical outcome.[30] It appears that reducing neointimal proliferation below a critical threshold, as measured, for instance, by late loss, may be sufficient to sustain a good clinical outcome. This implies that abolishing tissue in-growth is not indispensable for a good clinical outcome, as was shown for drug-eluting stents,[30] coated stents,[31] or bare metal stents in combination with oral immunosuppressive drug treatment.[32,33]

Safety Versus Efficacy

Issues related to potential tradeoffs between efficacy and safety of drug-eluting stents have received increasing attention in recent years.[16,17] The antiproliferative properties of drug-eluting stents are associated with delayed healing, which is setting the stage for prolonged biological interactions between the vessel wall and the permanent stent implantation. Side effects such as hypersensitivity reactions,[13] acquired late malapposition,[14] and most importantly, late stent thrombosis have been associated with delayed healing both in animal experiments[12] and in human observations.[11] Concerns about the prolonged risk of stent thrombosis have resulted in the empirical practice of extending dual antiplatelet therapy without alleviating the risk of abrupt thrombosis after treatment discontinuation.[15,17] Accepting a mild degree of in-stent neointimal proliferation that is still compatible with a good clinical outcome might offer a reasonable compromise between safety and efficacy while we await the development of drug-eluting stents with both antiproliferative and prohealing properties.[34]

Conversely, the question should be raised whether the antiproliferative properties of the Endeavor stent are sufficient to portend equally good clinical outcome when used in patient/lesion subsets with even higher propensity for restenosis.[35] The 3 principal determinants of restenosis after stenting are diabetes mellitus status, reference vessel diameter, and lesion length.[4–6,36–38] The zotarolimus-eluting stent reduced the risk of TLR in patients with and those without diabetes, although the number of patients with diabetes who required insulin was too small to permit subgroup analysis. The Endeavor stent also reduced TLR rates across subgroups in terms of vessel size and lesion length. Compared with the bare metal stent, the Endeavor stent was particularly effective in reducing TLR rates in small coronary arteries <2.5 mm in diameter (relative reduction, 57.0%) and lesions >16 mm (relative reduction, 57.1%). Thus, subgroup analysis of this trial suggests that the zotarolimus-eluting stent was effective in the lesion/patient subsets at moderate risk for restenosis included in the present trial.

Conclusions

The Endeavor stent can be recommended as a valuable new tool for the percutaneous treatment of coronary artery stenoses. The device is highly deliverable, has significant antirestenosis properties, and has a favorable safety profile with short-term dual antiplatelet therapy. The results of ongoing and future trials in high-risk subsets will provide further insights into the interplay between clinical outcome, antiproliferative effects, and patient safety.

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Disclosures

After completion of study performance and analysis, Dr Kuntz became an employee of Medtronic. Dr Bonan is a medical advisor of Medtronic, and Dr Ormiston has been a member of the Guidant Physician Advisory Board. Dr Kuck is a consultant for St Jude and Stereotaxis. Dr Popma is a member of the Medtronic Speakers' Bureau. Honoraria for lecturing at symposia have been received by Drs Fajadet (from Medtronic and Cordis J&J), Laarman (Medtronic and Cordis J&J), Kuck (St Jude and Biosense Webster), and Ormiston (Medtronic, Cordis J&J, Boston Scientific, and Guidant). Honoraria from Medtronic, Cordis J&J, Boston Scientific, Biotronik, and Conormed have been granted to the Cardiovascular Research Center Aalst on behalf of Dr Wijns. The institutions of Drs Wijns, Laarman, and Kuck are holding research grants from medical device companies. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

The safety and efficacy of the Endeavor zotarolimus-eluting phosphorylcholine polymer-coated stent were tested in a pivotal randomized clinical trial against bare metal stenting. Patients (n=1197) treated for single coronary artery stenosis were randomly assigned (1:1) to receive the Endeavor stent (n=598) or the same bare metal stent but without the drug or the polymer coating (n=599). The primary clinical end point of target vessel failure at 9 months was reduced from 15.1% with the bare metal stent to 7.9% with the Endeavor (P=0.0001). The rate of major adverse cardiac events was reduced from 14.4% with the bare metal stent to 7.3% with the Endeavor stent (P=0.0001). The rate of stent thrombosis was 0.5% with the Endeavor, which was not significantly different from 1.2% with bare metal stent. Differences in clinical outcome were maintained at 12 and 24 months (P<0.0001). In 531 patients submitted to angiographic follow-up, late loss was reduced from 1.03±0.58 to 0.61±0.46 (P<0.001) in stent and from 0.72±0.61 to 0.36±0.46 (P<0.001) in segment. Compared with bare metal stents, the Endeavor stent is safe and reduces the rates of clinical and angiographic restenosis at 9, 12, and 24 months.

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CLINICAL STUDIES

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Effect of High Dose Angiotensin-Converting Enzyme Inhibition on Restenosis: Final Results of the MARCATOR Study, a Multicenter, Double-Blind, Placebo-Controlled Trial of Cilazapril

DAVID P. FAXON, MD, FACC, ON BEHALF OF THE MULTICENTER AMERICAN RESEARCH TRIAL WITH CILAZAPRIL AFTER ANGIOPLASTY TO PREVENT TRANSLUMINAL CORONARY OBSTRUCTION AND RESTENOSIS (MARCATOR) STUDY GROUP

Objectives. We conducted a randomized, double-blind, placebo-controlled trial to assess the effect of low and high dose angiotensin-converting enzyme inhibition with cilazapril on angiographic restenosis prevention after percutaneous transluminal coronary angioplasty.

Background. Angiotensin-converting enzyme inhibitors possess antiproliferative effects in animal models of vascular injury. However, a recent clinical trial using low dose cilazapril, a long-acting angiotensin-converting enzyme inhibitor, failed to prevent restenosis.

Methods. Patients received either cilazapril (1 or 2.5 mg in the evening after successful coronary angioplasty, then 1, 5 or 10 mg twice daily for 6 months) or matched placebo. All patients received aspirin for 6 months. Coronary angiograms before and after angioplasty and at 6-month follow-up were quantitatively analyzed. In addition, the clinical, procedural and angiographic factors associated with restenosis were determined with the use of stepwise logistic analysis.

Results. A total of 1,436 patients with a successful coronary angioplasty were recruited. As assessed by an intention-to-treat analysis, the mean difference in minimal coronary lumen diameter (mean ± 1 SD) between the postangioplasty and follow-up angiogram at 6 months (primary end point) was −0.35 ± 0.51 for the placebo group and −0.37 ± 0.52, −0.45 ± 0.52 and −0.412 ± 0.53, respectively, for the 1-, 5- and 10-mg twice daily cilazapril groups (p = NS). Clinical events during follow-up did not differ among the four study groups. Multivariate analysis revealed only six variables as independent predictors of the loss of minimal lumen diameter: duration of angina <6 months, history of myocardial infarction, minimal lumen diameter before and after angioplasty as well as a proximal lesion location and reference diameters. Traditional risk factors for atherosclerosis did not relate to restenosis.

Conclusions. Long-term angiotensin-converting enzyme inhibition with cilazapril in high as well as low dosages does not prevent restenosis and does not favorably influence the overall clinical and angiographic outcome after coronary angioplasty. Few factors are predictive of restenosis.

(J Am Coll Cardiol 1995;2:362–9)

Despite the high primary success rate (>90%) (1) of percutaneous transluminal coronary angioplasty, the late restenosis rate (17% to 40%) still limits the long-term benefit of this procedure (2–5). Various studies (6–18) have attempted to determine the clinical and angiographic features that predict restenosis. Many of these have suffered from small numbers of patients or did not look at quantitative assessment of the change in lumen diameter. Some investigators (19–21) have suggested that quantification of lumen dimension changes over time reflects the biologic and mechanistic processes that operate during and after coronary angioplasty. A major advantage of this approach to patient evaluation is that it views restenosis as a continuous process. For this reason most recent restenosis trials with drugs have used this approach (22,23).

One of these was the MERCATOR trial (24), which assessed the effect of the long-acting angiotensin-converting enzyme inhibitor cilazapril. Using change in lumen diameter as the primary end point, this trial in 352 patients assigned to placebo and 341 patients assigned to cilazapril (5 mg twice daily) failed to show any detectable effect of the drug. A parallel study (MARCATOR) was conducted in the United States and Canada. This study differed in that three doses including a high dose were evaluated. This report contains confirmatory information on the lack of effect of both low and high dose cilazapril in inhibiting loss of lumen diameter. The large number of patients enrolled (1,436) and the detailed quantitative angiographic evaluation before and after coronary angioplasty and after 6 months allowed precise evaluation of the factors related to the change in lumen diameter after successful angioplasty.

Methods

Study group. Patients scheduled for coronary angioplasty meeting eligibility criteria were considered for inclusion in 41 participating centers (see Appendix). A total of 16,097 patients were considered for inclusion in the study and 1,436 of these

This study was sponsored by F. Hoffmann-La Roche Ltd., Basel and Cardiologique, Geneva, Switzerland. A complete list of the principal investigators and clinical sites of the MARCATOR study appears in the Appendix.

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were randomized. Patients were eligible for participation if they were between 25 and 80 years old and did not have a recent myocardial infarction (<5 days before randomization), severe valvular disease, severe hypertension, a prior revascularization procedure or recent treatment with an angiotensin-converting enzyme inhibitor.

Treatment allocation. The trial was carried out according to the declaration of Helsinki (1963) as revised in Venice (1983). After giving informed consent, patients having a successful coronary angioplasty (defined as a visually assessed diameter stenosis <50%) were randomly allocated to one of four study groups. Study medication was given within 6 h of the successful procedure and consisted of either 1) capsules of cilazapril (1 mg on the first evening, followed by 1 mg twice daily or 2.5 mg on the first evening followed by either 5 or 10 mg twice daily), or 2) matching placebo capsules for 6 months. In addition, all patients received aspirin (325 mg daily) starting before angioplasty and continuing until the time of follow-up.

Angioplasty procedure and angiographic analysis. At the beginning of the angioplasty procedure, all patients received heparin (intravenous bolus of 10,000 U and an intravenous infusion adjusted to maintain the activating clotting time >300 s). It was recommended that a calcium channel blocking agent be given before and for ≥24 h after angioplasty. The technical aspects of the procedure, including the choice of balloon, duration of balloon inflation and pressure, were determined by the individual angioplasty operator.

A coronary arteriogram was obtained just before and immediately after angioplasty and at follow-up. A standardized method of data acquisition (22–26) was used to ensure accurate reproducibility of the angiograms. All angiographic analyses, including qualitative assessment of certain lesion characteristics, were performed at a core laboratory whose workers were blinded to the treatment allocation and did not have access to clinical data.

All cineangiograms were quantitatively analyzed using the Cardiovascular Angiographic Analysis System (CAAS) system, as previously described, and in a manner similar to that used in the MERCATOR trial (22–26). The absolute values for the minimal lumen diameter as well as the reference diameter were measured by computer using known catheter diameter (in the absence of contrast medium) as a scaling device. Lesions with Thrombolysis In Myocardial Infarction (TIMI) grade ≤1 were assigned a value of 0 mm for minimal lumen diameter and 100% for grade ≤1 percent diameter stenosis. In these cases, the postangioplasty reference diameter was used as the reference diameter before angioplasty and at follow-up.

Follow-up evaluation. Patients returned for an outpatient evaluation after 1, 4, 12, 16 and 24 weeks. A clinical assessment including cardiac status, electrocardiogram (ECG) and a capsule count were performed at each visit. Laboratory tests and a symptom-limited exercise test were obtained at 4 and 24 weeks. Follow-up angiography was performed at the 24-week visit after the trial medication had been discontinued for 24 h. If symptoms recurred before 24 weeks, coronary angiography was carried out at that time. If no definite restenosis was present and the follow-up time was <3 months, the patient was asked to undergo repeat coronary angiography at 6 months.

End points. The primary end point of this study was the change in minimal lumen diameter as determined by quantitative angiography after coronary angioplasty and at the 24-week follow-up time point. If a clinical condition required repeat angioplasty at an earlier time period, the angiogram made before repeat angioplasty was used to obtain follow-up values, irrespective of the timing of the repeat study.

The minimal lumen diameter for each segment dilated was recorded as the mean value from multiple matched projections unless multiple views were not available. The change in minimal lumen diameter was determined as the follow-up value minus the postangioplasty value. When more than one segment was dilated, the mean change over all lesions dilated was taken as the end point. Secondary end points were restenosis rates and clinical events. The clinical events collected during the 6-month follow-up period included death; New York Heart Association functional class III or IV due to congestive heart failure; nonfatal myocardial infarction; coronary revascularization (coronary bypass surgery or repeat angioplasty); recurrent angina (Canadian Cardiovascular Society class II or higher) requiring initiation or increase in medical therapy; or none of the above. A myocardial infarction was defined as the occurrence of typical symptoms, ECG changes and elevated creatine kinase levels twice the upper limit of normal. All myocardial infarctions were adjudicated by a critical events committee that had no knowledge of drug assignment. Only coronary revascularization procedures that were performed before the 6-month time window (24 ± 3 weeks) were counted as a clinical event.

Statistical methods and analyses. The planned sample size per group was 350. Accounting for adverse events and withdrawal, it was expected that at least 293 evaluable patients per group would be available for analysis. The necessary sample size is based on the assumption of restenosis rates of 30% in the placebo group and 20% in the combined cilazapril groups (a 33% improvement with treatment), as well as on a two-sided significance level of 5%. Under these assumptions the study has a power of 80%.

The intention-to-treat analysis included all patients who took at least one dose of test medication and had an analyzable baseline angiogram after a successful angioplasty procedure. If a follow-up angiogram was absent, the minimal lumen diameter at follow-up was imputed according to the following rules: In case of death, nonfatal myocardial infarction or coronary artery bypass graft surgery, follow-up minimal lumen diameter was imputed as 0. In all other cases it was calculated by using the average postangioplasty minimal lumen diameter for all patients who had an analyzable angiogram. The per-protocol population group was defined as patients who were ≥80% compliant with treatment, had an analyzable follow-up angiogram and adhered to the protocol.

Differences in baseline characteristics among the study groups were tested by using conventional parametric or non-

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Table 1. Clinical Characteristics of the Total Patient Group at Baseline

	Placebo + Aspirin (n = 361)	Cilazapril 1 mg Twice Daily + Aspirin (n = 359)	Cilazapril 5 mg Twice Daily + Aspirin (n = 361)	Cilazapril 10 mg Twice Daily + Aspirin (n = 355)
Male	298 (83%)	295 (82%)	294 (81%)	266 (75%)
Age (yr)				
Mean ± SD	57.5 ± 9.9	58 ± 10	58.5 ± 9.9	58.2 ± 10.4
Range	35–80	29–78	33–79	27–83
Current smoker	77 (21%)	82 (23%)	68 (19%)	67 (19%)
Diabetes	43 (12%)	36 (10%)	57 (16%)	65 (18%)
CCS angina class III or IV	212 (59%)	203 (56%)	196 (55%)	204 (57%)
Pain at rest	150 (42%)	176 (49%)	156 (43%)	170 (48%)
Duration of angina (days)	356	357	340	357
Previous MI	174 (48%)	141 (39%)	168 (47%)	175 (49%)
Total cholesterol (mmol/liter)	5.6	5.4	5.4	5.5

Unless otherwise indicated, data are presented as number (%) of patients. CCS = Canadian Cardiovascular Society; MI = myocardial infarction.

parametric tests as appropriate. The minimal lumen diameter before and after coronary angioplasty and at follow-up were examined separately, as well as the change in minimal lumen diameter using analysis of covariance, with minimal lumen diameter before angioplasty as the covariate. Clinical benefit of trial medication was analyzed by using the Mantel-Haenszel chi-square statistic.

A stepwise logistic analysis was performed by using baseline clinical, procedural and angiographic variables to determine those factors independently related to the change in minimal lumen diameter. The analysis was done on a per patient basis, as well as a per lesion basis. In the per patient analysis, if more than one lesion was dilated, the procedural and angiographic variables were averaged. In addition, variables derived from the first analysis were checked to see whether they also had an influence on the occurrence of restenosis, (defined as >50% stenosis at follow-up).

The study protocol closely paralleled that of the MERCATOR trial with similar entry criteria and identical angiographic assessment. The study design differed from that of the MERCATOR trial by its randomization of patients after the angiographic procedure rather than before and its inclusion of postmyocardial infarction patients (>5 days) and patients with insulin-dependent diabetes. The trial was monitored by a steering committee and overseen by a data and safety monitoring board that had full access to all patient data.

Results

A total of 1,436 patients gave informed consent and were randomly assigned to the four treatment groups. Two patients, one in the placebo and one in the 10-mg twice daily cilazapril group, did not have an adequate baseline angiogram and were excluded from the intention-to-treat analysis. One hundred sixty-nine patients were not compliant with study medication, 159 did not have an adequate follow-up angiogram and 22 had a protocol violation. Thus, 75% of the patients were included in the per-protocol study group.

Baseline characteristics and clinical follow-up. The baseline characteristics were similarly distributed between the placebo and combined cilazapril groups (Table 1). Of note was a high percentage of patients with pain at rest in all groups. Risk factors, current smokers, hypertension, elevated cholesterol and diabetes were frequently encountered in all groups.

Procedural characteristics also did not differ among the groups (Table 2). Multiple dilations were performed in <25% of patients. The left anterior descending coronary artery was the most frequently dilated vessel. The balloon/artery ratio and total duration of balloon inflation also did not differ among groups.

Clinical follow-up was obtained in all patients. The outcome of the patient groups is shown in Table 3. During the 6-month follow-up period, eight patients died (one placebo-treated and six cilazapril-treated patients three, two and two in the 1-, 5- and 10-mg twice daily groups, respectively); the cause of death was cardiovascular in all but one patient. Nonfatal myocardial infarction was documented in 35 patients. A total of 261 underwent coronary revascularization with coronary angioplasty or bypass surgery and 118 had recurrent angina not resulting in intervention. Two thirds of the patients were event free at the 6-month follow-up time point. Adjusted chi-square test revealed no difference in events between the placebo and cilazapril groups. No differences were noted when only the per-protocol population was analyzed.

Of the 169 patients who were not compliant with treatment because they had an adverse experience, 33 were withdrawn because of severe hypotension and 21 for severe cough. The most common reason for withdrawal was the recurrence of angina pectoris (range 10% to 14% per group).

Angiographic efficacy analysis. Table 4 summarizes the quantitative angiographic findings in the intention-to-treat

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Table 2. Procedural Characteristics for Patients in the Intent-to-Treat Analysis

	Placebo + Aspirin (n = 360)	Cilazapril 1 mg Twice Daily + Aspirin (n = 359)	Cilazapril 5 mg Twice Daily + Aspirin (n = 361)	Cilazapril 10 mg Twice Daily + Aspirin (n = 354)
Multiple dilations	82 (23%)	74 (21%)	79 (22%)	83 (23%)
Lesions dilated (no.)	464	457	472	460
Vessel dilated				
RCA	158 (34%)	156 (34%)	175 (37%)	177 (39%)
LAD	185 (40%)	174 (38%)	188 (40%)	162 (35%)
LCx	121 (26%)	127 (28%)	109 (23%)	121 (26%)
Balloon/artery ratio	1.13 ± 0.17	1.13 ± 0.19	1.12 ± 0.18	1.10 ± 0.17
Total inflation time (s)	378	371	384	354

Unless otherwise indicated, data are presented as number (%) of patients or mean value ± SD. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

group. Missing values were imputed as described before. The loss in minimal lumen diameter at follow-up was −0.353 mm for the placebo group and −0.367, −0.449 and −0.412, respectively, for the 1-, 5- and 10-mg twice daily cilazapril-treated patients (p = NS). The results were similar in the per-protocol treatment group. Figures 1 and 2 show the cumulative frequency curves for minimal lumen diameter and the change in minimal lumen diameter for the placebo and cilazapril groups; again, no group differences were noted. The restenosis rates according to the seven frequently used restenosis criteria (3) did not differ among groups. With restenosis defined as >50% stenosis at follow-up, 33% of the placebo group demonstrated restenosis as did 40%, 36% and 34%, respectively, of the groups treated with cilazapril, 1, 5 or 10 mg twice daily.

Multivariate analysis. The stepwise multiple linear regression analysis was performed by using the change in minimal lumen diameter (follow-up minimal lumen diameter minus postangioplasty minimal lumen diameter) as the dependent variable. Forty-one clinical and angiographic variables were entered into the model. Two analyses were conducted (Table 5). The first utilized the change in minimal lumen diameter per patient to evaluate patient-related variables. Six variables (two clinical and four angiographic) were found to be independently related to restenosis. In a separate analysis, only lesion variables were assessed and eight variables were found to be important. Four variables were significant in both analyses. In the lesion analysis, plaque area (17), a quantitative angiographic assessment of the volume of plaque extending into the lumen, and a symmetry index (17), a quantitative angiographic assessment of the symmetry of the stenosis, were also importantly related to loss in minimal lumen diameter. The number of inflations was the only procedural variable associated with the loss of minimal lumen diameter. In the per-lesion analysis, the presence of a postprocedural coronary dissection was also important. However, the degree of the dissection as defined by the coding system of the National Heart, Lung, and Blood Institute (27) did not influence this relation. This is probably due to a small number of severe dissections in this trial because patients who were considered to have had unsuccessful angioplasty by angiography or who developed a major complication immediately after angioplasty were excluded.

The ability of these models to predict the loss in minimal lumen diameter was poor; <10% of the change in minimal lumen diameter was accounted for by the identified variables. Because the change in minimal lumen diameter may not directly relate to the development of a significant stenosis at follow-up, many investigators have defined restenosis as >50% stenosis at follow-up. When the identified variables were tested to determine if they were also predictive of restenosis by this definition, all variables except the mean reference diameter in

Table 3. Clinical Outcome for the Total Patient Group

	Placebo + Aspirin (n = 361)	Cilazapril 1 mg Twice Daily + Aspirin (n = 359)	Cilazapril 5 mg Twice Daily + Aspirin (n = 361)	Cilazapril 10 mg Twice Daily + Aspirin (n = 355)
Death	1 (<1%)	3 (<1%)	2 (<1%)	2 (<1%)
Congestive heart failure	7 (2%)	1 (<1%)	1 (<1%)	1 (<1%)
Myocardial infarction	8 (2%)	9 (2%)	8 (2%)	10 (3%)
Revascularization	54 (15%)	72 (20%)	62 (17%)	73 (21%)
Recurrent angina	50 (14%)	48 (13%)	46 (13%)	37 (10%)
Event free	241 (67%)	226 (63%)	242 (67%)	232 (65%)

All data are presented as number (%) of patients.

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Table 4. Quantitative Analysis Results for Patients in the Intent-to-Treat Analysis

	Placebo + Aspirin (n = 360)	Cilazapril 1 mg Twice Daily + Aspirin (n = 359)	Cilazapril 5 mg Twice Daily + Aspirin (n = 361)	Cilazapril 10 mg Twice Daily + Aspirin (n = 354)
Minimal lumen diameter (mm)				
Before PTCA	0.97 ± 0.38	0.96 ± 0.37	0.97 ± 0.39	0.98 ± 0.35
After PTCA	1.72 ± 0.36	1.70 ± 0.34	1.74 ± 0.36	1.75 ± 0.36
Follow-up	1.37 ± 0.56	1.34 ± 0.56	1.29 ± 0.57	1.34 ± 0.55
Reference diameter (mm)*				
Before PTCA	2.63 ± 0.53	2.60 ± 0.50	2.64 ± 0.51	2.67 ± 0.53
After PTCA	2.69 ± 0.51	2.68 ± 0.51	2.68 ± 0.50	2.72 ± 0.51
Follow-up	2.72 ± 0.58	2.68 ± 0.55	2.67 ± 0.53	2.71 ± 0.60
Diameter stenosis (%)				
Before PTCA	62.5 ± 13.9	62.2 ± 14.1	62.9 ± 13.8	62.5 ± 13.0
After PTCA	35.3 ± 8.3	36.0 ± 7.8	34.8 ± 8.2	34.9 ± 7.9
Follow-up	48.4 ± 17.9	48.5 ± 18.4	50.5 ± 19.7	48.8 ± 17.9

*Or in patients with follow-up angiogram (total occlusions not included). All values are presented as mean value ± SD. PTCA = percutaneous transluminal coronary angioplasty.

the patient analysis and all variables except the symmetry index and the number of inflations in the lesion analysis were found to be important.

Discussion

The results of this multicenter, double-blind, randomized trial confirm the finding of the European MERCATOR trial (24) that the angiotensin-converting enzyme inhibitor cilazapril does not reduce restenosis after successful coronary angioplasty. They extend those findings by demonstrating that high dose cilazapril (twice the dose used in the European trial) is also ineffective. Nevertheless, oral therapy with this angiotensin-converting enzyme inhibitor was well tolerated in the patients studied.

There are many potential reasons for the lack of an effect of cilazapril on restenosis. Previous animal studies have shown that angiotensin II infusion can lead to smooth muscle cell proliferation and that angiotensin-converting enzyme inhibition results in a dose-dependent reduction in intimal hyperplasia after vascular injury in some animal models (28,29). It is possible that the pathophysiologic events that lead to intimal hyperplasia and restenosis in animal models are not the same as those that lead to restenosis in humans; therefore, angiotensin II may play a much less important role in humans. The lack of benefit to date shown in nearly all clinical trials of drugs to prevent restenosis also raises concerns about the validity of the animal models used to study the restenosis process (30). Restenosis is a multifactorial process and attempts to prevent

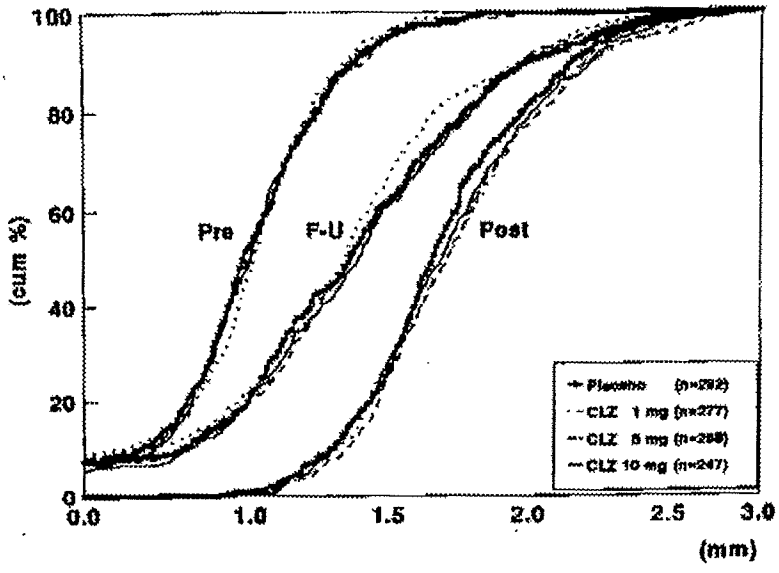

Figure 1. Cumulative distribution curve (cum %, Y axis) of the minimal lumen diameter (X axis) for the four study groups (placebo and 1, 5 and 10 mg twice daily of cilazapril [CLZ]) before (Pre) and after (Post) angioplasty and at follow-up (F-U). No differences among groups were present at any time.

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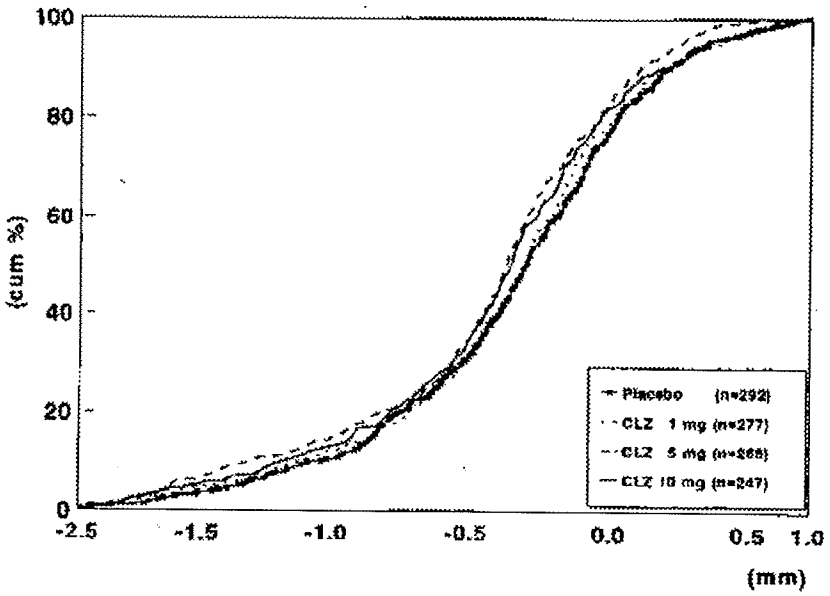

Figure 2. Cumulative distribution curve of the change in minimal lumen diameter for the four study groups. No difference was evident among groups. Abbreviations as in Figure 1.

it by a single agent focused on a single process may be inadequate. In addition, experimental studies (31) suggest that high doses of agents are necessary to prevent restenosis. Although the dose of cilazapril used in this trial was high, it may have been insufficient to inhibit intimal hyperplasia. Data extrapolated from animal studies (29,30) suggest that the dose needed to prevent restenosis may be ≥10 times greater than that used in our study. We chose not to use a cilazapril dose >10 mg twice daily because safety studies of a higher dose regimen have not been conducted in humans. We also began therapy immediately after coronary angioplasty to maximize enrollment and minimize potential hypotensive complications during the angioplasty procedure. Experimental studies (29) suggest that pretreatment for ≥1 week before vascular injury may increase the effectiveness of angiotensin-converting enzyme inhibition. Given these limitations of our trial, it remains possible that angiotensin-converting enzyme inhibition in humans might reduce restenosis if higher dose therapy and pretreatment could be given.

Table 5. Multivariate Stepwise Analysis for the Prediction of Loss in Minimal Lumen Diameter

Variable	Estimate	SEE
Patient Analysis		
Duration of angina >6 mo	−0.10	0.03
Minimal lumen diameter		
Before PTCA	−0.20	0.04
After PTCA	+0.57	0.05
Proximal location	+0.06	0.03
Reference diameter	−0.16	0.04
History of myocardial infarction	+0.06	0.03
Lesion Analysis		
Minimal lumen diameter		
Before PTCA	−0.25	0.06
After PTCA	+0.66	0.05
Reference diameter	−0.27	0.04
Plaque area	+0.01	0.01
Symmetry	+0.16	0.06
Proximal location	+0.09	0.03
Dissection	−0.13	0.03
Number of balloon inflations	+0.02	0.01

PTCA = percutaneous transluminal coronary angioplasty.

Factors influencing the loss in minimal lumen diameter. Quantitative angiographic studies have shown that restenosis is a process that narrows the vessel lumen in nearly all patients (19), although <25% of patients develop recurrent symptoms severe enough to require reintervention (20). For the purpose of clinical trials, restenosis may be best defined as a continuous variable as assessed by change in lumen diameter, which is more sensitive than other markers as an indicator of the underlying biologic process (21). Even though we evaluated restenosis in this way, we failed to show benefit from cilazapril. However, the large size of this clinical trial and the detailed quantitative angiographic assessment provide a unique opportunity to evaluate the factors that contribute to the loss of minimal lumen diameter.

A stepwise logistic analysis identified several clinical and angiographic variables that related to restenosis. *In the patient analysis*, only two clinical variables were found to predict restenosis: duration of angina <6 months and a history of prior myocardial infarction. Both of these variables are known to be associated with intracoronary thrombosis, and these findings support a relation between thrombosis and restenosis (32). The most important predictors of restenosis in this study were

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angiographic and included the minimal lumen diameter before and after coronary angioplasty. A large lumen before coronary angioplasty reflects a less severe coronary stenosis, whereas a large lumen after angioplasty indicates a large change in the percent stenosis or a large initial gain. These observations are consistent with previous work (21) suggesting that a greater increase in minimal lumen diameter at the time of angioplasty (immediate gain) is associated with a greater late loss in lumen diameter at the time of follow-up or, as commonly stated, "the more you gain, the more you lose." However, as in previous studies, the gain/loss ratio in our study was <1, indicating that the net gain was positive and supportive of an opposing concept: "bigger is better" (33). We also found that the reference diameter and a proximal lesion location were factors in predicting late lumen loss.

In a second analysis evaluating only lesion variables, the same angiographic variables that were identified in the patient analysis were again found to be significant. In addition, lesion symmetry, plaque area and the number of balloon inflations were also related to loss in minimal lumen diameter. The variables identified in both of these analyses were also highly related to restenosis when restenosis was defined as >50% stenosis at follow-up.

Predictors of restenosis. Although many studies (5–18) have evaluated risk factors for restenosis, most have suffered from a small sample size, a selection bias such that only patients who returned for restudy were analyzed, or use of less sensitive definitions of restenosis. Only the Coronary Artery Restenosis Prevention on Repeated Thromboxane Antagonism Study (CARPORT) trial (34) and the MERCATOR trial (35) share with our study the absence of these limitations. Thus, it is not surprising that our findings, in contrast to those of several previous studies (6–16), do not point to the importance of clinical variables and risk factors in predicting restenosis. Previous investigators (6–10) have suggested that male gender, hypercholesterolemia and cigarette smoking are all important risk factors for restenosis. However, more recent work utilizing quantitative angiography (14,15,17,35) is consistent with our finding that lesion variables, particularly the degree of narrowing before and after the procedure, are the most important factors predicting subsequent restenosis. Our study also is consistent with several previous studies showing that the duration of angina is related to restenosis. However, in contrast to the study by Rensing (17) and Weintraub (18) and their coworkers but consistent with the work of Bourassa et al. (14), our study found no relation between the percent change in lumen diameter and the presence of diabetes. Again, in contrast to Rensing et al. (17), we were unable to demonstrate that thrombosis after angioplasty was related to restenosis. This finding may be due to our exclusion of patients who developed a complication during the 1st 6 h after angioplasty.

The relation between restenosis and stenosis severity or minimal lumen diameter before angioplasty has been well described (6–15). Likewise, minimal lumen diameter after angioplasty is also related to restenosis. When restenosis is defined as the change in minimal lumen diameter, the relation is positive; when it is defined as >50% stenosis at follow-up, the relation is reversed and restenosis is decreased when minimal lumen diameter is larger immediately after angioplasty. These findings reflect the advantage of a large postprocedural lumen diameter (33) and support the view that "bigger is better." The presence of a coronary dissection after the procedure was associated with less restenosis, as others (16) have shown. The mechanism of this effect remains unclear, but it might be related to the type of atherosclerosis within the vessel wall. A more fibrocalcific plaque is more likely to dissect than is a soft plaque and, because of its relative lack of cellularity, it may be less prone to restenosis (36).

Study limitations. Although this study identified several clinical and angiographic factors that were associated with restenosis, these variables had a poor predictive value. Prior studies by Rensing, Weintraub and Hermans and their coworkers (17,18,35) support these findings and suggest that additional factors not measured in these studies may be more influential. Because angiography only measures lumen compromise and not the underlying biologic process, the poor predictive ability is not surprising. The pathophysiologic events are complicated and may be related more to the degree of the vascular injury and the nature of the atheroma than to the patient or angiographic factors. Further studies utilizing techniques that more precisely evaluate the arterial wall and its response to injury may give us further insights into the factors responsible for restenosis.

Summary. Our study demonstrates that cilazapril in doses ranging from low to high did not reduce restenosis in a large multicenter, double-blind, placebo-controlled clinical trial. The study was able to define several clinical and angiographic factors that relate to restenosis. These factors should help identify high risk patients and help to further understanding of restenosis.

Appendix

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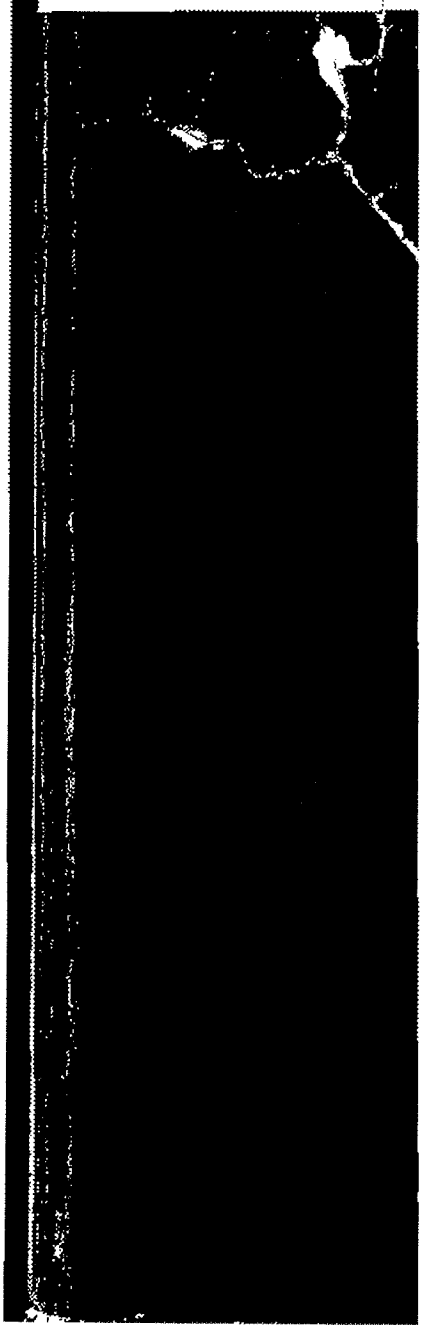

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Brief Communications

Clinical Investigation and Reports

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Low Molecular Weight Heparin in Prevention of Restenosis After Angioplasty

Results of Enoxaparin Restenosis (ERA) Trial

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Background Heparin, an anticoagulant, possesses antiproliferative effects and has been shown to reduce neointimal proliferation and restenosis following vascular injury in experimental studies.

Methods and Results The primary aim of this double-blind multicenter study was to determine if 40 mg Enoxaparin, a low molecular weight heparin, administered subcutaneously once daily for 1 month after successful angioplasty would reduce the incidence of restenosis. Four hundred fifty-eight patients were randomized at nine clinical centers (231 to placebo and 227 to Enoxaparin). The primary end point was angiographic or clinical restenosis. Angiographic restenosis was defined as a loss of 50% of the initial gain as measured by quantitative coronary angiography (QCA) at a core laboratory. In the absence of QCA, clinical evidence of restenosis was defined as death, myocardial infarction, repeat revascularization, or worsening angina. Using the intention-to-treat analysis for all patients, restenosis occurred in 51% of the placebo group and 52% of the Enoxaparin group (relative risk, 1.07, $P=.625$). Likewise, no difference in restenosis was evident when the change in minimal lumen diameter or other angiographic definitions of restenosis were used. Adverse clinical events were infrequent and did not differ between the groups with the exception of minor bleeding complications, which were more common in the Enoxaparin group.

Conclusions Enoxaparin (40 mg/d SC for 1 month) following successful angioplasty did not reduce the incidence of angiographic restenosis or the occurrence of clinical events over 6 months. The treatment was well tolerated, although in-hospital minor bleeding was more common with active treatment. (*Circulation.* 1994;90:908-914.)

Key Words • heparin • restenosis • angioplasty • clinical trials

Coronary angioplasty is estimated to have been performed in more than 300 000 patients in 1991.[1] Since its inception, the success of the procedure has steadily improved, and the incidence of short-term complications has decreased.[2] However, the long-term outcome has continued to be complicated by restenosis. Angiographic evidence of restenosis occurs in 30% to 50% of patients after a successful procedure and necessitates a repeat procedure in 20% to 25% of patients.[3]

Experimental studies suggest that restenosis is a physiological response to severe vascular injury and is analogous to the process of generalized wound healing.[4] Angioplasty stretches the vascular wall, often tearing the neointimal plaque.[5] Immediately after dilatation, elastic recoil occurs with subsequent deposition of platelets and formation of thrombus.[6] Smooth muscle cell proliferation and matrix formation repair the damaged vessel, resulting in a final remodeling of the lumen. In an effort to reduce the incidence of restenosis, a number of drugs have been evaluated, including antiplatelets, antithrombotics, calcium antagonists, omega-3 fatty acids, angiotensin-converting enzyme inhibitors, steroids, and anti-inflammatory drugs.[7] To date, no agent has been shown to be effective in preventing this process.

Heparin has pharmacological properties that are potentially useful in reducing restenosis. Not only does it have anticoagulant and antithrombotic effects, but it has also been shown to prevent neointimal proliferation in vitro as well as in animal models of vascular injury.[8-20] Enoxaparin is a low molecular weight heparin (approximately 4500 d) obtained by partial and controlled depolymerization of a benzyl ester of porcine mucosal heparin.[21] Compared with heparin, Enoxaparin provides approximately three times greater anti-Xa activity than anti-IIa activity. It also has a significantly longer half-life and has proven to be effective in the prevention of deep vein thrombophlebitis when given subcutaneously once or twice daily.[22-24] The purpose of this multicenter trial was to evaluate whether Enoxaparin given subcutaneously daily for 28 days after successful angioplasty would reduce the incidence of restenosis as determined by angiography and by the occurrence of clinical signs and symptoms.

Methods

All patients at nine clinical centers were screened for eligibility between May 1989 and August 1990. Patients were considered if they were 21 years of age or older and had a successful angioplasty performed. A successful procedure was defined as a >50% stenosis reduced to <30% stenosis with a ≥20% change in diameter. Measurements were made using hand-held calipers by the principal investigator or his designee at each clinical center. Patients were excluded if they met one

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of the following criteria: woman of childbearing potential, history of bleeding disorders or recent active bleeding, uncontrolled asthma or hypertension (blood pressure >180/105 mm Hg), active peptic ulcer disease, history of heparin-associated thrombocytopenia, acute myocardial infarction within 5 days, abrupt vessel closure after angioplasty, or other complications requiring heparin therapy for >24 hours after percutaneous transluminal coronary angioplasty (PTCA). A left main artery stenosis of >50%, angioplasty of a saphenous vein graft, or prior PTCA at the same site also were exclusion criteria. The PTCA was performed using standardized techniques as previously reported. Angiography before and immediately after angioplasty was performed after intracoronary nitroglycerin administration. The two orthogonal views that best identified the lesions were recorded for subsequent quantitative coronary analysis at a core laboratory.

Patients meeting qualifying criteria were approached for informed consent before PTCA and were randomized to receive either placebo or Enoxaparin (40 mg SC daily for 28 days) after a successful procedure. The drug was begun 2 hours after femoral sheath removal and was administered no later than 24 hours after the procedure. Heparin was administered during the PTCA procedure and adjusted to maintain the activated clotting time at >300 seconds. Acetylsalicylic acid (325 mg PO QD) was administered 1 day before and throughout the treatment period. Patients were instructed in subcutaneous administration of the study drug by a trained study nurse at each clinical site. Calcium antagonists were administered before and after PTCA but were discontinued unless considered clinically necessary by the investigator. In general, patients were discharged from the hospital 1 or 2 days after angioplasty.

Patients returned at 1, 4, and 24 weeks after angioplasty for clinical and bleeding assessment. Laboratory assessment measured at each time point included complete blood count, coagulation profile, and liver function tests. A treadmill exercise test using the modified Bruce protocol was obtained before and at 1 and 24 weeks after randomization. ST-segment changes and exercise duration were recorded. All patients returned for repeat coronary angiography 24±4 weeks after randomization. Angiography was again performed using 7F or 8F catheters after administration of intracoronary or intravenous nitroglycerin. The two optimal orthogonal views previously identified to best demonstrate the stenosis were repeated.

The angiograms were sent to the core angiographic laboratory at Baylor College of Medicine. Each film was viewed by a trained technician who was blinded to patients' therapy. Each projection optimally demonstrating the target lesion was identified. The pre-PTCA, post-PTCA, and follow-up angiograms were analyzed using the Coronary Angiographic Analysis System (CAAS) as previously described.[24-26] The stenosis and proximal and distal segments were manually identified and then digitized using a semiautomated edge-detection system. Two views were used when possible, and the minimal lumen diameter, percent area stenosis, and reference diameters were calculated. Ten percent of the angiograms were rereviewed in a blinded fashion as part of a quality control assessment. All films demonstrating >0.2-mm difference in reference diameter were reanalyzed. When more than one lesion was dilated, the average of all dilated lesions for that patient was used in the analysis. Other angiographic data, including ejection fraction, number of vessels diseased, and morphology, were determined by the investigators at each clinical site.

Clinical assessment included the occurrence of death, myocardial infarction, emergency or elective bypass surgery, emergency or elective PTCA, unstable angina, occurrence of angina, or worsening of angina on effort by two or more grades as defined by Canadian Cardiovascular Society anginal classification. Myocardial infarction was determined by the investigator at each site and defined as two or more of the three following criteria: new pathological Q waves, chest pain of >30 minutes' duration, and elevation of creatinine phosphokinase (CPK) to more than twofold the normal level associated with elevated CPK-MB fraction.

TABLE 1. Patient Analysis Groups

Patient Group	Patients Receiving Placebo, n (%)	Patients Receiving Enoxaparin, n (%)	Total, n (%)
Randomized	231	228	459
Not treated	0	1	1
All treated	231 (100)	227 (>99)	458 (>99)
Evaluable	176 (76)	181 (79)	357 (78)

In addition, bleeding was assessed and quantified as major or minor. Major bleeding was defined as a clinically evident bleeding episode associated with a decrease in hemoglobin of at least 2 g/dL and/or requiring transfusion of at least 2 U of blood. Any intracerebral or retroperitoneal bleed was considered a major bleed. The site and source of bleeding episodes were noted.

The primary end point of the trial was a loss of 50% of the initial gain in lumen diameter achieved at angioplasty or clinical evidence of restenosis. This angiographic definition is also known as the National Heart, Lung, and Blood Institute (NHLBI) IV PTCA definition.[3] In the absence of angioplasty, clinical evidence of restenosis was defined as death, myocardial infarction, repeat revascularization, or worsening angina. Other angiographic categorical definitions of restenosis as well as the change in minimal lumen diameter were also analyzed.[3] Additional efficacy assessment included the presence of >0.1 mV of ST-segment depression and exercise duration on the exercise stress test and clinical events including worsening angina, death, myocardial infarction, bypass surgery, and angioplasty.

Statistical Analysis

The primary analysis of efficacy used the intention-to-treat principle. The demographic variables were compared, but statistical analyses were not performed. For the efficacy analysis, justification for pooling across centers was investigated using a two-way logistical regression model (PROC CATMOD) with factors for treatment group, center, and treatment by center investigated. Treatment comparisons were based on a .05 significance level, the odds ratio of treatment failure was computed, and the 95% confidence intervals were determined. The incidence of treatment failure in the subgroups was also calculated. The change in minimal lumen diameter was analyzed as a continuous variable. For patients who had more than one lesion dilated, the average minimal lumen diameter of all lesions successfully dilated was used for this analysis. A weighted analysis for mean change in minimal lumen diameter of a lesion was also performed.

Results

Patient Analysis Groups

The all-treated patient group included all patients who received at least one dose of the study medication (Table 1). The "evaluable" patient group included all treated patients who also had angiography performed at 26±12 weeks after randomization or earlier if warranted by recurrence of angina or clinical symptoms and had study medication administered within 36 hours of successful PTCA and had received a minimum of 22 doses.

Baseline Characteristics

The baseline demographic characteristics of all treated patients are given in Tables 2 and 3. Two hundred thirty-one patients were randomized to receive placebo and 227 patients to receive Enoxaparin. The two groups did not differ in any baseline clinical or angiographic characteristic. In general, the patients had multivessel

TABLE 5. Quantitative Angiographic Results for All Treated Patients

	Patients Receiving Placebo			Patients Receiving Enoxaparin		
Study Period	No Lesions	Reference Diameter, mm	MLD, mm	No Lesions	Reference Diameter, mm	MLD, mm
Before angioplasty	235	2.84	0.84	227	2.87	0.81
After angioplasty	235	2.87	1.94	227	2.89	1.96
Follow-up	235	2.76	1.45	227	2.88	1.43
Initial gain			1.10		1.15	
Late loss			−0.49		−0.54	(*P*=NS)

MLD indicates minimal lumen diameter.

patients with initially positive exercise test, or single-lesion PTCA. No differences were seen between treated and placebo patient groups in these subgroups.

Angiographic Restenosis

The change in minimal lumen diameter and reference diameter—before PTCA, after PTCA, and at follow-up—is shown in Table 5 for all lesions in the evaluable patients for whom follow-up angiography was available. The acute gain in minimal lumen diameter was 1.10 mm for the placebo group and 1.15 mm for the Enoxaparin group. The late loss in lumen diameter was 0.49 mm and 0.54 mm, respectively (P=.78). The cumulative distribution of the minimal lumen diameter before PTCA, immediately after PTCA, and at follow-up similarly showed no differences between groups (Figs 2 and 3) and followed a gaussian distribution as has been reported by others.[28] Likewise, analysis of incidence of angiographic restenosis by lesion for all patients with a follow-up angiogram is given in Table 6. The five commonly used categorical definitions also showed no differences. Other postprocedural characteristics, including dissection, were not different, although few dissections were present as a result of the strict entry inclusion and exclusion criteria.

Clinical Outcome

As shown in Table 7, serious adverse outcomes were rare, with death, myocardial infarction, and emergency bypass surgery occurring in five placebo patients and eight Enoxaparin patients. The most common event was the presence of asymptomatic angiographic restenosis using the NHLBI IV definition. Asymptomatic angiographic restenosis occurred in 29% of the placebo group and 27% of the Enoxaparin group. Of interest is that only 17% of the placebo group and 16% of the Enoxaparin group developed significant angina, suggesting that a sizable percentage of the patients had silent restenosis. Subsequent revascularization with bypass surgery or angioplasty was infrequent (9% of the placebo group and 12% of the Enoxaparin group) and probably is due to the low incidence of angina in both patient groups. However, this incidence of revascularization may also be artificially low as the performance of angioplasty or surgery was not recorded after completion of 24 weeks of follow-up.

Exercise testing using the modified Bruce protocol at both 1 week and follow-up was performed in 205 placebo and 205 Enoxaparin patients. Analyzable modified Bruce protocol exercise tests were not consistently obtained at each time point, making comparisons between groups difficult. A comparison of the 109 patients in the placebo group and the 106 patients in the Enoxaparin group in whom adequate paired exercise tests were obtained showed no differences in anginal ST-segment changes. Seventeen percent of the placebo group and 12% of the Enoxaparin group developed exercise-induced angina at follow-up, whereas 20% and 24%, respectively, developed new ST-segment depressions at the 24-week exercise test. Again, these data may be skewed as patients who developed clinical evidence of restenosis earlier during follow-up did not have a 24-week exercise test.

Bleeding Complications

The overall incidence of major and minor bleeding was 34% in the placebo group and 48% in the Enox-

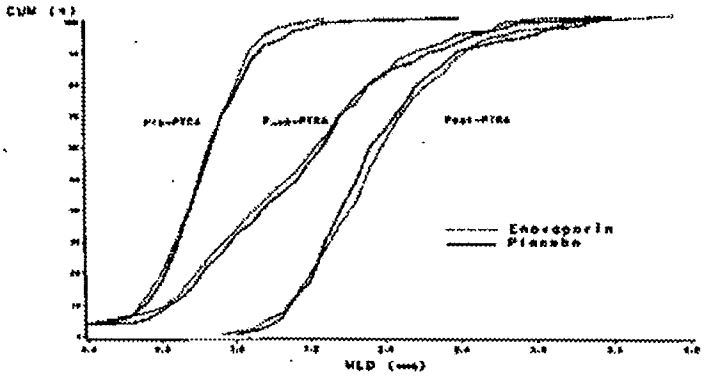

FIG 2. Plot of minimal lumen diameter (MLD) measured by quantitative coronary angiography before angioplasty (PTCA), after PTCA, and at follow-up is shown for all patients who had an evaluable end point angiogram. No differences were seen between the Enoxaparin and control groups.

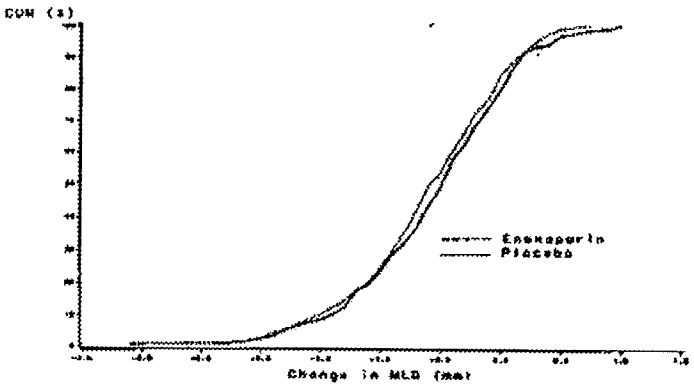

FIG 3. Plot of change in minimal lumen diameter (MLD) between the follow-up angiogram and the immediately post-percutaneous transluminal coronary angioplasty angiogram. No between-group differences were present.

aparin group ($P<.0008$). This difference primarily was confined to minor bleeding episodes. There were no episodes of intracerebral or retroperitoneal bleeding, and all except one major bleed occurred at the femoral arterial entry site. Nearly all major and minor groin bleeding occurred during the initial hospital stay.

Other adverse events were infrequent and did not differ between groups. Of importance, platelet count, liver function tests, prothrombin time, and partial thromboplastin time as well as cholesterol levels were not significantly different.

Discussion

The results of the present study demonstrate that Enoxaparin, a low molecular weight heparin, given for 28 days after angioplasty did not reduce the incidence of restenosis or reduce adverse clinical outcomes when compared with placebo. It did, however, result in an increase in bleeding complications. These complications were usually minor, occurred at the arterial entry site during the initial hospitalization, and were easily managed by usual medical methods.

Restenosis is a multifactorial process that involves elastic recoil, platelet deposition, thrombus formation, inflammation, smooth muscle cell proliferation, and matrix organization.[4-7] Heparin is used routinely during angioplasty to prevent a thrombotic abrupt vessel closure. However, it is also recognized to have antiproliferative actions that may be useful in preventing restenosis.[8-20]

Heparin was initially isolated from porcine mucosa and was shown to have anticoagulant and antithrombotic properties.[8] The mechanism of this action was later demonstrated to be dependent on binding to antithrombin III, resulting in a conformational change that allows antithrombin III to bind avidly with factors IIa and Xa. Heparin is a sulfonated glycosaminoglycan and is a mixture of chain lengths that results in molecular weights ranging from 5000 to 50 000 d. In 1977, Clowes and Karnovsky[9] demonstrated that heparin inhibited neointimal proliferation in a rat injury model. Subsequently, a number of studies have shown that heparin can reduce experimental intimal hyperplasia by 30% to 60%.[8-20] Cell culture studies have demonstrated that the antiproliferative properties are greater for the lower molecular weight heparins and are independent of its ability to bind antithrombin III.[14] Thus, the nonanticoagulant fractions are as effective as the anticoagulant fractions in prevention of neointimal proliferation. The antiproliferative effect is dose dependent. Although the exact mechanism of action of heparin in preventing cell proliferation is not known, heparin and its analogues appear to block the cell cycle at the G_1 stage.[15] Incorporation into the cell nucleus appears to be important in its antiproliferative actions. In addition, heparin can bind and alter growth factor activity.[16] A related form of heparin, heparan sulfate is a naturally

TABLE 6. Incidence of Angiographic Restenosis Perfusion for All Patients With a Follow-up Angiogram

Definition*	Patients Receiving Placebo, n (%)	Patients Receiving Enoxaparin, n (%)
No. of patients	192	202
NHLBI I (≥30% increase)	57 (30)	65 (32)
NHLBI II (<50% to >70%)	33 (17)	44 (21)
NHLBI III (≤10% before stenosis)	40 (21)	44 (21)
NHLBI IV (loss 50% gain)	97 (51)	106 (52)
<50% to >50%	86 (45)	87 (43)

NHLBI indicates National Heart, Lung, and Blood Institute.
*Angiographic definitions of restenosis are provided in Reference 3.

TABLE 7. Adverse Clinical Outcomes for All Treated Patients

Clinical Outcome	Patients Receiving Placebo, n (%)	Patients Receiving Enoxaparin, n (%)	Overall, n (%)
Death	1 (<1)	1 (<1)	2 (<1)
MI	4 (2)	5 (2)	9 (2)
Emergency CABG	0	2 (<1)	2 (1)
Elective CABG	2 (1)	2 (<1)	4 (1)
Emergency PTCA	5 (3)	7 (3)	12 (3)
Elective PTCA	10 (5)	17 (8)	27 (7)
Unstable angina	4 (2)	1 (<1)	5 (1)
Occurrence or worsening of angina	33 (17)	33 (16)	66 (17)
Asymptomatic restenosis	56 (29)	54 (27)	110 (28)
No evidence of restenosis	77 (40)	81 (40)	158 (40)

MI indicates myocardial infarction; CABG, emergency coronary artery bypass surgery; and PTCA, percutaneous transluminal coronary angioplasty.

TABLE 6. Bleeding Complications, Thrombocytopenia, and Injection Site Hemorrhage for All Treated Patients

Clinical Event	Patients Receiving Placebo, n (%)	Patients Receiving Enoxaparin, n (%)	P	Overall, n (%)
Major bleed*	6 (2)	14 (5)	.058	20 (3)
Groin	67	94		161 (35)
Nasal	3	0		3
Genitourinary	2	2		4
Gastrointestinal	1	2		3
Other	3	1		4
Thrombocytopenia	7 (3)	9 (4)		16 (3)
Injection site hemorrhage	13 (6)	35 (15)	<.001	48 (21)
Decrease in hemoglobin >2 g/dL	16 (7)	21 (9)	37 (8)	

*Major bleed was bleeding resulting in death, clinically overt with a decrease in hemoglobin of ≥2 g/dL, or a transfusion of ≥2 U red blood cells or was retroperitoneal or intracranial.

occurring glycosaminoglycan that is a constituent of the extracellular matrix of the arterial wall.[19] It is believed that this compound may provide a important cell regulatory action within the arterial wall.

Enoxaparin, a low molecular weight heparin, differs from regular heparin in a number of ways.[21] It is generated from heparin by chemical depolymerization and has an average molecular weight of 4500 d. Due to the shorter chain length, it has approximately three times more anti-Xa activity than anti-IIa activity in contrast to the 1:1 ratio for heparin. Importantly, its half-life as measured by anti-Xa activity is 4.6 hours compared with 2.95 hours for heparin; however, anti-Xa activity can be measured for as long as 24 hours after a single dose.[22] Experimental studies using a hypercholesterolemic rabbit model have demonstrated a dose-dependent reduction in restenosis using Enoxaparin once daily.[20]

The present study represents the first report of the sustained use of a low molecular weight heparin to prevent restenosis in humans. Ellis et al[29] reported that an 18- to 24-hour infusion of heparin immediately after PTCA did not prevent restenosis in a randomized trial of 416 patients. Three brief reports of heparin in restenosis have been published.[30-33] In one study using Fragmin, a low molecular weight heparin, a significant trend toward a reduction in restenosis was seen.[31] A preliminary brief report of a randomized trial of 10 000 U heparin SC once daily compared with placebo was prematurely discontinued because of a high incidence of adverse events and angiographic restenosis.[29] One potential explanation for the high incidence of treatment failure seen in this trial may be the drug-dosing regimen. Because 10 000 U heparin SC was given daily, it is possible that a heparin rebound may have occurred. As reported in this trial, no significant increase in adverse events or restenosis was documented with the use of subcutaneous low molecular weight heparin. This may well be due to lack of rebound because of its longer half-life. Two other large trials using low molecular heparin are under way (FACT and EMPAR trials).

Study Limitations

There are a number of study limitations. The lack of an effect on restenosis in this trial does not exclude the possibility that Enoxaparin prevents restenosis in humans. In our study, we chose to begin Enoxaparin after angioplasty. Experimental studies have shown that pretreatment can significantly increase the effectiveness of heparin as an antiproliferative agent.[34] We chose to start the drug after PTCA for several reasons. Experimental studies have shown that heparin is effective even if administered after injury.[16] In addition, pretreatment could increase the risk of periprocedural bleeding. An additional limitation is the low dose of heparin given in this study. The antiproliferative effect of heparin is well documented to be dose dependent,[5-20,34] and the relation between heparin's anti-Xa activity and proliferation is uncertain. Although direct extrapolation of doses between studies in animals and humans is hazardous, prior animal studies suggest that extremely high doses were necessary to achieve the desired effect. The doses used in this trial were the highest previously studied doses that have been shown to be safe and effective in the prevention of deep vein thrombophlebitis in patients undergoing high-risk orthopedic surgery.[22] Although higher doses may have been effective, concerns about safety precluded using doses equal to those studied experimentally. Finally, the duration of therapy (28 days) may not have been sufficient. However, experimental studies suggest that therapy need be given only during the proliferative phase, which is estimated to extend to the first few weeks after injury.[16] It is possible, however, that proliferation occurs beyond this time point and that a longer duration of therapy may have been necessary to reduce restenosis. Many of these limitations are being addressed in other current clinical trials of heparin and low molecular weight heparin in the prevention of restenosis. Finally, it is possible that mechanisms other than intimal hyperplasia are important in restenosis. Experimental studies and intravascular ultrasound studies in humans suggest that late remodeling may be more important than intimal hyperplasia in causing restenosis.[34,35]

Heparin and related compounds, such as Enoxaparin, possess anticoagulant and antiproliferative effects that make them attractive therapeutic agents for the prevention of restenosis. Although this study demonstrates no effect on the prevention of restenosis, further study is warranted. High-dose, local delivery or combination therapy with other agents may be needed to inhibit this complex process.

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Appendix

Enoxaparin Investigators

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Editorials

Brief Rapid Communication

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Editorial

Polymer Coatings for Stents

Can We Judge a Stent by Its Cover?

Tim A. Fischell, MD

The article by van der Giessen et al[1] in this issue of *Circulation* provides an important perspective on the challenges associated with the development of a truly biocompatible polymeric stent coating.

See p 1690

A number of investigators have worked diligently over the past several years to explore the feasibility of a completely bioabsorbable stent.[2] The impetus for this approach was the perception that the long-term implantation of metallic stents might provide a chronic inflammatory stimulus and/or lead to medial atrophy with aneurysm formation that could negate the immediate- and intermediate-term (6 months) advantages of stenting compared with the use of balloon angioplasty in the coronary circulation.[3,4] However, recent studies have suggested that concerns about "late" restenosis and aneurysm formation with metallic stents in atherosclerotic human coronary arteries are likely unfounded.[5] The excellent long-term biocompatibility of stainless steel stents, combined with the substantive difficulties in developing a polymeric stent with a high-performance delivery system, radiopacity, and competitive structural characteristics (eg, radial hoop strength) have led previously enthusiastic polymer stent proponents to focus their efforts on developing biocompatible polymeric coatings for metal stents. Such a hybrid device (metal backbone plus polymer coating) would provide the mechanical advantages of stenting, including reduction in early elastic recoil and the elimination of unfavorable late remodeling, and at the same time provide a platform for local drug delivery to decrease stent thrombogenicity and/or neointimal hyperplasia.

Although appealing in concept, the potential difficulties in the successful development of a biocompatible hybrid (polymer/metal) stent are highlighted by the present study. In this study using an animal model performed at three leading interventional cardiology centers, the investigators examined the histological responses to five biodegradable (polyglycolic acid/polylactic acid, polycaprolactone, polyhydroxybutarate valerate, polyorthoester, and polyethylenoxide/polybutylene terephthalate) and three nonbiodegradable (polyurethane, silicone, and polyethylene terephthalate) polymers applied to a 90° arc of the balloon-expandable Wiktor tantalum stent. These particular polymers were selected due to their potential for excellent biocompatibility based on previous in vitro and in vivo testing.[1] The vessel wall responses at the (noncoated) tantalum wire implantation sites were used as the control and compared with the histopathological responses seen surrounding the polymer. The authors found that all of the implanted polymer coatings were associated with a significant inflammatory and exaggerated neointimal proliferative response. In addition, their data suggest that at least some of the polymer coatings may have provoked an enhanced thrombotic response.

As pointed out by the authors, the inflammatory response evoked by these polymers demonstrates the limitations of screening compounds with the use of in vitro or subcutaneous implant assays for biocompatibility. The intravascular environment is indeed unforgiving and does not readily tolerate foreign bodies. In addition to the usual tissue biocompatability issues, the exposure to flowing blood with the potential for activation of platelets, the extrinsic clotting cascade, or both provide a challenge to identify a compound that could be used in a hybrid stent design without aggravating the thrombotic risks. These challenges are exaggerated in the coronary circulation due to the potential for enhanced platelet activation at high shear rates in smaller vessels.[6] In the present study, the potentially prothrombotic behavior of the polymer-coated stents may be only partially attributable to the polymer per se. One of the limitations of the present study was that the polymer was applied in a nonuniform manner with a comparatively thick layer (75 to 125 μm). The rheology of such a thick and eccentric polymer coating may have predisposed the polymer-coated segment to platelet activation and thrombus formation. In a study by De Scheerder et al,[7] who used a thinner (23 μm) and more uniformly applied polyurethane stent coating, there appeared to be a favorable effect on stent thrombosis. In the present study, the possibility that the marked inflammatory response observed with most of the polymers may also have contributed to enhance the thrombogenicity of these stents cannot be excluded.

Although the results of the present study raise concerns regarding an exaggerated thrombogenic potential for polymer-coated stents, the recently reported in vivo and clinical experience with the polymer-coated (polyamine plus dextran sulfate trilayer) Palmaz-Schatz stent with covalently bound heparin from the Benestent II trial suggests that it is possible to find a biocompatible polymeric coating that, when combined with an active agent (eg, heparin), can be successfully used to reduce the throm-

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bogenic potential of stents.[8,9] The success of this particular coating may be related to the biocompatibility of this polymer, the very thin and uniform application of the coating, and the antithrombin and secondary antiplatelet effects of the covalently bound heparin.

The acute and chronic inflammatory responses and the accelerated neointimal proliferative responses observed with all of the polymers in the present study raise important questions with regard to the use of a polymer-coated stent as a drug-delivery vehicle to inhibit neointimal hyperplasia. These data should, however, be interpreted with the caveat that the stents used were not sterilized and may have harbored nonbacterial or, less likely, bacterial pyrogens.

There are several challenges to the development of a stent coating that will inhibit neointimal hyperplasia. If a biodegradable compound is chosen as the drug delivery vehicle, the degradation of such a compound is typically mediated by a low-level inflammatory response. Such an inflammatory response is mediated by macrophages, lymphocytes, and other inflammatory cell subtypes and has the capability to incite greater neointimal hyperplasia and negate some or all of the antiproliferative effect of the "drug." Although there may be a theoretical advantage to the use of a nonbiodegradable polymer as a reservoir for drug delivery, the present study demonstrates that the use of nonbiodegradable polymers does not necessarily eliminate the potential for inflammation and an associated aggravation of the neointimal hyperplastic response after stenting. The other challenge to the development of a hybrid stent to inhibit restenosis is related to the choice of the active agent (drug). Despite a wealth of potential drugs that might be incorporated into the ideal, but yet-to-be-identified, noninflammatory polymer, it remains unclear which agent, if any, can be delivered locally in adequate concentrations and over an appropriate period of time to achieve a favorable antiproliferative effect. If and when a promising drug/polymer/stent combination is developed, the regulatory pathway for the approval of such a combination of device plus drug is likely to be an arduous one. We should not expect to see such a device available for widespread clinical use in the near future.

Finally, although the eight agents tested in the present study appear to be problematic, other polymers, such as a high-molecular-weight poly-L-lactic acid,[2] fibrin,[10] and the polyamine plus dextran sulfate trilayer coating used in the recent Benestent II trial[9] show some promise. Newer drug choices, including nitric oxide synthase or nitric oxide donors may prove to have desirable antiplatelet and antiproliferative properties.[11] Other hybrid stent concepts, including a β-particle–emitting radioisotope stent, with P32 incorporated beneath the surface of a metal stent, also show promise as a method of modulating the neointimal proliferation observed after stenting.[12,13] Ultimately, the clinical results obtained through the use of these hybrid stent technologies will need to be compared in terms of efficacy, time efficiency, and cost efficiency with conventional stenting and with other approaches, including stenting plus local drug delivery, stenting plus catheter-based irradiation, and systemic delivery of potent antiplatelet agents such as c7E3.[14]

Despite the negative results of the present study, the concept of a hybrid stent composed of a state-of-the-art metallic backbone with a thin layer of a biocompatible polymeric coating containing an active agent to inhibit thrombosis and/or restenosis remains appealing. In the future, it is likely that we will evaluate stents not only by their ease of delivery and structural characteristics but also by their long-term biocompatibility, antithrombogenicity, and antiproliferative capabilities.

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KEY WORDS • Editorials • stents • biocompatibility • polymers

A RANDOMIZED COMPARISON OF CORONARY-STENT PLACEMENT AND BALLOON ANGIOPLASTY IN THE TREATMENT OF CORONARY ARTERY DISEASE

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Abstract *Background.* Coronary-stent placement is a new technique in which a balloon-expandable, stainless-steel, slotted tube is implanted at the site of a coronary stenosis. The purpose of this study was to compare the effects of stent placement and standard balloon angioplasty on angiographically detected restenosis and clinical outcomes.

Methods. We randomly assigned 410 patients with symptomatic coronary disease to elective placement of a Palmaz–Schatz stent or to standard balloon angioplasty. Coronary angiography was performed at base line, immediately after the procedure, and six months later.

Results. The patients who underwent stenting had a higher rate of procedural success than those who underwent standard balloon angioplasty (96.1 percent vs. 89.6 percent, P = 0.011), a larger immediate increase in the diameter of the lumen (1.72±0.46 vs. 1.23±0.48 mm, P<0.001), and a larger luminal diameter immediately after the procedure (2.49±0.43 vs. 1.99±0.47 mm, P<0.001). At six months, the patients with stented lesions continued to have a larger luminal diameter (1.74±0.60 vs. 1.56±0.65 mm, P = 0.007) and a lower rate of restenosis (31.6 percent vs. 42.1 percent, P = 0.046) than those treated with balloon angioplasty. There were no coronary events (death; myocardial infarction; coronary-artery bypass surgery; vessel closure, including stent thrombosis; or repeated angioplasty) in 80.5 percent of the patients in the stent group and 76.2 percent of those in the angioplasty group (P = 0.16). Revascularization of the original target lesion because of recurrent myocardial ischemia was performed less frequently in the stent group than in the angioplasty group (10.2 percent vs. 15.4 percent, P = 0.06).

Conclusions. In selected patients, placement of an intracoronary stent, as compared with balloon angioplasty, results in an improved rate of procedural success, a lower rate of angiographically detected restenosis, a similar rate of clinical events after six months, and a less frequent need for revascularization of the original coronary lesion. (N Engl J Med 1994;331:496-501.)

THE long-term benefit of coronary balloon angioplasty is limited by the possibility of restenosis of the treated segment, which occurs in approximately 30 to 50 percent of patients.[1-4] Restenosis can be caused by several factors, including elastic recoil of the dilated artery, platelet-mediated thrombus formation, proliferation of smooth-muscle cells, and vascular remodeling.[5] When restenosis develops, it is frequently associated with recurrent myocardial ischemia that necessitates additional revascularization procedures. New approaches to coronary intervention have therefore been developed with the aim of reducing the possibility of restenosis. Debulking coronary atheroma with lasers or atherectomy has not improved the problem of restenosis.[6-9] However, preliminary evidence suggests that stents may reduce the chance of restenosis by decreasing the elastic recoil of the vessel and sealing intimal flaps, thus providing a wider, smoother coronary lumen.[10,11] To test this hypothesis, we conducted a prospective, randomized trial to compare the rates of restenosis with coronary-stent placement and standard balloon angioplasty.

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*Additional participants in the Stent Restenosis Study (STRESS) trial are listed in the Appendix.

METHODS

Participating Centers and Investigators

The study centers and investigators were selected on the basis of their experience with implantation of Palmaz–Schatz coronary stents. The study protocol was approved by the institutional review board at each of the 20 centers participating in the trial.

Patient Selection

The study population consisted of patients with symptomatic ischemic heart disease and new lesions of the native coronary circulation. The specific angiographic criteria for enrollment included at least 70 percent stenosis, according to the estimate of the investigators; a lesion that was 15 mm or less in length and could be spanned by a single stent; and a vessel diameter of at least 3.0 mm. The criteria for exclusion were a myocardial infarction within the previous seven days; a contraindication to aspirin, dipyridamole, or warfarin sodium; and a left ventricular ejection fraction of 40 percent or less. The angiographic criteria for exclusion were evidence of coronary thrombus, the presence of multiple focal lesions or diffuse disease, serious disease in the left main coronary artery, ostial lesions, and severe vessel tortuosity.

Randomization

After the patients had been interviewed to determine their eligibility and had given their informed consent, they were randomly

assigned to either stent placement or balloon angioplasty. Randomization of the patients, stratified according to center with a block design, was carried out by means of sealed envelopes. The randomization sequence was developed so that an equal number of patients would be assigned to each treatment at each center.

Procedural Protocol

Stent Placement

The Palmaz–Schatz stent is composed of two rigid 7-mm slotted stainless-steel tubes connected by a 1-mm central bridging strut (Johnson and Johnson Interventional Systems, Warren, N.J.). The stent, which is 1.6 mm in diameter in the unexpanded state, is mounted on a balloon catheter and protected by an outer sheath during passage to the target site. When the sheath is withdrawn, inflation of the balloon catheter expands the stent. Technical details of the design and placement of the Palmaz–Schatz coronary stent have been described elsewhere.[12,13]

Patients assigned to stent placement received nonenteric aspirin (325 mg daily), dipyridamole (75 mg three times a day), and treatment with a calcium-channel antagonist, initiated at least 24 hours before the procedure. In addition, patients received intravenous low-molecular-weight dextran (dextran 40, given at a dose of 100 ml per hour for two hours before stenting and at a dose of 50 ml per hour during and after the procedure, for a total volume of 1 liter). During the procedure, patients received an initial bolus injection of heparin (10,000 to 15,000 units) supplemented as needed to maintain an activated clotting time of more than 300 seconds. The heparin infusion was discontinued at the termination of the procedure and reinstituted four to six hours after hemostasis of the site of vascular access had been achieved. Warfarin sodium was begun on the day of the procedure. Heparin and warfarin sodium were both administered for at least 72 hours or until a prothrombin time of 16 to 18 seconds had been achieved (international normalized ratio, 2.0 to 3.5). After patients were discharged from the hospital, dipyridamole and warfarin sodium were continued for one month, and aspirin was continued indefinitely.

Angioplasty Protocol

Angioplasty was performed with the use of conventional techniques. Aspirin was prescribed, but warfarin sodium was not administered. Investigators attempted to achieve an optimal result with balloon angioplasty, which was defined as residual stenosis of less than 30 percent of the luminal diameter, according to a visual estimate. A crossover to stent placement was permitted as a "bail-out" procedure in the case of abrupt or threatened closure, defined as a dissection of the artery with compromised antegrade blood flow (Thrombolysis in Myocardial Infarction [TIMI] grade, <3) or persistent stenosis of over 50 percent of the luminal diameter in association with evidence of myocardial ischemia (chest pain, electrocardiographic changes, or both).

Follow-up

Patients were required to have clinical follow-up studies after one, three, and six months. Coronary angiography was required at six months in all the patients except those who had died or undergone coronary-artery bypass surgery or repeated angioplasty for abrupt closure during the first 14 days after the initial revascularization. Angiography performed before four months was allowed on the basis of clinical indications. However, if restenosis was not found, a subsequent angiogram was obtained after four months.

Angiographic Analysis

Angiography was performed in two orthogonal views. Intracoronary nitroglycerin (200 mg) was injected before all angiographic assessments. Angiograms were analyzed at the Core Angiographic Laboratory at Jefferson Medical College. Quantitative analysis was performed with the use of a validated edge-detection algorithm.[14] Vessel edges were determined with the computerized algorithm, and luminal diameters were measured with the dye-filled catheter as a reference. The diameters of the normal segments proximal and distal to the treated area were averaged to determine the reference diameter. The minimal luminal diameter, reference diameter, and percentage of stenosis were calculated as the mean values from two orthogonal projections. The percentage of elastic recoil was defined as the largest inflated-balloon diameter minus the postprocedural minimal luminal diameter divided by the inflated-balloon diameter. In addition, coronary lesions were assessed for eccentricity, calcification, thrombus, plaque ulceration, tortuosity, and postprocedural dissection. Definitions used for this morphologic analysis and prior validation studies of the quantitative angiographic analysis have been described elsewhere.[11,13,15]

End Points

The primary end point of the trial was angiographic evidence of restenosis, defined as at least 50 percent stenosis on the follow-up angiogram. Secondary angiographic end points included angiographic evidence of procedural success and the absolute minimal luminal diameter after the procedure and at follow-up. Angiographic evidence of procedural success was defined as a reduction in stenosis to 50 percent or less by quantitative analysis.

Clinical evidence of procedural success was defined as angiographic evidence of success without a major complication (death, myocardial infarction, or coronary-artery bypass surgery) during the index hospitalization. The secondary clinical end point was a composite end point, defined as whichever of the following occurred first: death, myocardial infarction, coronary bypass surgery, or the need for repeated angioplasty within the first 6 months (±60 days) after the initial revascularization. Myocardial infarction was documented by the presence of new Q waves of at least 0.04 second's duration or a creatine kinase level or MB fraction at least twice the upper limit of normal. Clinical events were classified as early (occurring from day 0 to day 14) or late (occurring after 14 days). Revascularization of the target lesion was defined as angioplasty or bypass surgery performed because of restenosis of the target lesion in association with recurrent angina, objective evidence of myocardial ischemia, or both. Other events included abrupt vessel closure (after the patient had left the catheterization laboratory) and hemorrhagic complications, defined as a cerebrovascular accident, bleeding requiring transfusion, or the need for vascular surgery.

Clinical and angiographic data were forwarded to the Data Coordinating Center at the University of Pittsburgh for statistical analyses. Adverse events were audited and reviewed by members of the Steering Committee. The primary analysis of angiographic and procedural outcomes was based on the intention-to-treat principle. We also performed a secondary analysis of the rate of restenosis according to the treatment received.

For the analysis of continuous data, two-tailed t-tests were used to assess differences between the two treatment groups. The results are expressed as means ±SD. Categorical data, which are presented as rates, were compared by chi-square test, except for the composite clinical end point and revascularization of the target lesion, which were analyzed by means of Kaplan–Meier survival curves, with differences between the two treatment groups compared by Wilcoxon test.[16] Multiple linear regression was used to assess the relation between the luminal diameter at follow-up and multiple clinical and angiographic variables, including age, sex, location of the lesion, vessel diameter, and postprocedural luminal diameter.

Results

Between January 1991 and February 1993, 410 patients were enrolled in the study; 207 patients were randomly assigned to stent placement, and 203 to angioplasty. After randomization, three patients (two in the stent group and one in the angioplasty group) were excluded because they did not meet all the enrollment criteria. Thus, the final study group comprised 407 patients. Their base-line clinical and angiographic characteristics are shown in Table 1. More

men were assigned to the stent group than to the angioplasty group, and the patients in the stent group had lesions that were slightly longer, with a higher incidence of eccentricity, but the two groups were well matched with respect to other clinical characteristics.

Procedural and Early Clinical Outcome

Stents were placed in 197 of the 205 patients (96.1 percent) randomly assigned to this therapy. One patient, in whom stent placement failed because of an inability to cross the lesion with a guide wire, was treated medically. Seven patients were switched to angioplasty: three because of an inability to place the stent and four because of lesion characteristics deemed unfavorable for stent placement at the time of the procedure. In the angioplasty group, six patients required emergency coronary-artery bypass surgery. In addition, 15 patients were switched to alternative therapies: 14 (6.9 percent) to emergency stent placement as a bailout procedure (1 of the 14 subsequently required emergency bypass surgery) and 1 to directional atherectomy.

Table 1. Base-Line Clinical and Angiographic Characteristics of Patients Assigned to Stent Placement or Angioplasty.*

Characteristic	Stent Group (N = 205)	Angioplasty Group (N = 202)
Male — % of patients	83	73†
Age — yr	60±10	60±10
Diabetes — % of patients	15	16
Hypertension — % of patients	43	45
Hyperlipidemia — % of patients	44	48
Current smoker — % of patients	21	24
History of myocardial infarction — % of patients	37	36
Recent myocardial infarction (within previous 6 wk) — % of patients	18	15
Unstable angina — % of patients	47	48
Pain at rest	33	39
Pain with electrocardiographic changes	23	26
Postinfarction angina	7	6
No. of diseased vessels — % of patients		
1	64	68
2	27	21
3	9	11
Ejection fraction — %	61±12	61±11
Target vessel — % of patients		
Left anterior descending	47	48
Left circumflex	16	13
Right coronary artery	37	39
Calcification — % of patients	17	15
Thrombus — % of patients		
Definite	2	1
Possible	15	9
Eccentricity — % of patients	66	54‡
Lesion angulation >45° — % of patients	13	18
Lesion length — mm	9.6±3.0	8.7±2.7§
Stenosis — % of luminal diameter	75±9	75±8

*Plus–minus values are means ±SD.
†P<0.05.
‡P = 0.02.
§P<0.001.

Table 2. Procedural Outcomes and Clinical Events.

Variable	Stent Group (N = 205)	Angioplasty Group (N = 202)	P Value
	% of patients		
Procedural outcome			
Angiographic success			
Reading at study center	99.5	96.5	0.04
Quantitative analysis	99.5	92.6	<0.001
Clinical success	96.1	89.6	0.011
Early events (0–14 days)			
Death	0	1.5	0.12
Myocardial infarction/Q wave	5.4/2.9	5.0/3.0	0.85/1.0
Coronary bypass surgery	2.4	4.0	0.38
Abrupt closure*	3.4	1.5	0.34
Repeated angioplasty	2.0	1.0	0.69
Any event	5.9	7.9	0.41
Late events (15–240 days)			
Death	1.5	0	0.25
Myocardial infarction/Q wave	1.5/1.0	2.0/0.5	0.72/1.0
Coronary bypass surgery	2.4	4.5	0.26
Repeated angioplasty	9.8	11.4	0.59
Target-vessel revascularization	10.2	15.4	0.06
Any event	15.1	15.8	0.84
All events (0–240 days)			
Death	1.5	1.5	0.99
Myocardial infarction/Q wave	6.3/3.4	6.9/3.5	0.81/0.9
Coronary bypass surgery	4.9	8.4	0.15
Repeated angioplasty	11.2	12.4	0.72
Any event	19.5	23.8	0.16
Bleeding and vascular complications			
Cerebrovascular accident	1.0	0.5	1.0
Surgical vascular repair	3.9	2.0	0.25
Bleeding requiring transfusion	4.9	2.5	0.11
Any event	7.3	4.0	0.14

*After the patient left the catheterization laboratory.

Procedural and early clinical outcomes are shown in Table 2. According to the quantitative analysis there was angiographic evidence of procedural success in 204 of the 205 patients (99.5 percent) randomly assigned to undergo stent placement and in 187 of the 202 patients (92.6 percent) randomly assigned to undergo angioplasty (P<0.001). The clinical success rates were 96.1 percent and 89.6 percent, respectively (P = 0.011).

Abrupt vessel closure occurred in 10 patients after they had left the catheterization laboratory: 7 in the stent group and 3 in the angioplasty group (3.4 and 1.5 percent, respectively; P = 0.34). In the three patients in the angioplasty group, the closure occurred after the stent had been placed as a bailout measure. Abrupt closure occurred an average of 6 days (range 2 to 14) after the procedure, and in 6 of the 10 patients, it occurred after hospital discharge. All the patients with abrupt closures had major cardiac events (two died and eight had nonfatal myocardial infarctions). The proportions of patients with any major cardiac event (death, myocardial infarction, coronary bypass surgery, or repeated angioplasty within 14 days after the procedure) were 5.9 percent in the stent group and 7.9 percent in the angioplasty group

(Table 2). Bleeding and vascular complications occurred more commonly in the stent group than in the angioplasty group (7.3 percent vs. 4.0 percent, P = 0.14). The hospital stay after the procedure was longer in the stent group (5.8 days vs. 2.8 days, P<0.001).

Angiographic Results

Angiography was repeated at six months in 336 of the 383 patients (88 percent) eligible for follow-up. Angiography was not repeated in 28 patients in the stent group because of refusal (15 patients) or ineligibility due to stent thrombosis (7), death (3), early coronary bypass surgery (2), or inability to perform the study procedures (1). In the angioplasty group, 43 patients did not have follow-up angiography because of refusal (32) or ineligibility due to early coronary bypass surgery (7), abrupt vessel closure (3), or death (1). The rate of restenosis was 31.6 percent (56 of 177 patients) in the stent group and 42.1 percent (67 of 159) in the angioplasty group (P = 0.046). The rates of restenosis among the patients who received their assigned therapy were 30.0 percent in the stent group and 43.0 percent in the angioplasty group (P = 0.016).

The luminal dimensions at base line, immediately after the procedure, and at follow-up are shown in Table 3. At base line, there was no difference in the reference diameter or the severity of stenosis between the two groups. After the procedure, a larger immediate gain in the luminal diameter was achieved in the patients who underwent stent placement than in those who underwent angioplasty, resulting in a larger mean (±SD) diameter in the stent group (2.49±0.43 vs. 1.99±0.47 mm, P<0.001). At follow-up, the stent group had a larger mean reduction in the luminal diameter (0.74±0.58 vs. 0.38±0.66 mm, P<0.001) but a larger net gain, resulting in a larger luminal diameter at follow-up (1.74±0.60 vs. 1.56±0.65 mm, P = 0.007). These data are shown in Figure 1. A stepwise linear regression analysis showed that the luminal diameter immediately after the procedure was the most important predictor of the luminal diameter at six months (b = 0.41, P<0.001), irrespective of the procedure used. Additional important determinants included a larger reference diameter (b = 0.31, P<0.001) and location of the lesion in a vessel other than the left anterior descending coronary artery (b = 0.14, P = 0.029).

Late Clinical Follow-up

Data on late cardiac events and all events are shown in Table 2. Clinical follow-up data were available for 406 of the 407 patients. Although the numbers of patients who died or had myocardial infarctions were comparable in the two groups, fewer patients in the stent group underwent revascularization of the target lesion (10.2 percent vs. 15.4 percent, P = 0.06) (Fig. 2). Event-free survival was 80.5 percent in the stent group, as compared with 76.2 percent in the angioplasty group (P = 0.16) (Fig. 3). Among the patients eligible for follow-up, a larger proportion of those in the stent group remained free of angina (78.9 percent vs. 71.1 percent, P = 0.076).

Table 3. Angiographic Results in the Stent and Angioplasty Groups.*

Variable	Stent Group (N = 205)	Angioplasty Group (N = 202)	P Value
Before the procedure			
Reference vessel (mm)	3.03±0.42	2.99±0.50	0.30
Minimal luminal diameter (mm)	0.77±0.27	0.75±0.25	0.48
Stenosis (% of luminal diameter)	75±9	75±8	0.81
After the procedure			
Reference vessel (mm)	3.05±0.40	2.99±0.46	0.15
Minimal luminal diameter (mm)	2.49±0.43	1.99±0.47	<0.001
Stenosis (% of luminal diameter)	19±11	35±14	<0.001
Elastic recoil (%)	15±11	24±15	<0.001
Dissection (% of patients)	7	25	<0.001
At follow-up			
Reference vessel (mm)	3.00±0.41	2.98±0.49	0.74
Minimal luminal diameter (mm)	1.74±0.60	1.56±0.65	0.007
Stenosis (% of luminal diameter)	42±18	49±19	0.001
Restenosis (% of patients)	31.6	42.1	0.046
Change in minimal luminal diameter			
Immediate gain (mm)	1.72±0.46	1.23±0.48	<0.001
Late loss (mm)	0.74±0.58	0.38±0.66	<0.001
Net gain (mm)	0.98±0.62	0.80±0.63	0.01

*Plus–minus values are means ±SD. Immediate gain refers to the minimal luminal diameter immediately after the procedure minus the diameter before the procedure. Late loss refers to the minimal luminal diameter immediately after the procedure minus the diameter at follow-up. Net gain refers to the minimal luminal diameter at follow-up minus the diameter before the procedure.

Discussion

In this trial, we compared stent placement with balloon angioplasty for the treatment of new focal coronary stenoses in larger vessels; we found a reduc-

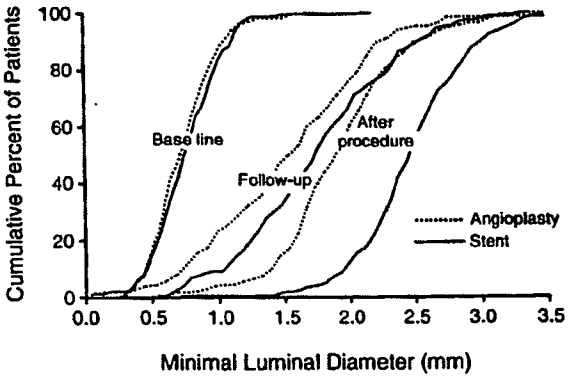

Figure 1. Minimal Diameter of the Lumen at Base Line, Immediately after Stent Placement or Angioplasty, and at Follow-up.

There was no difference in base-line values between the stent and angioplasty groups. Immediately after the procedure, the patients in the stent group had a larger minimal luminal diameter than those in the angioplasty group. Six months later, both groups had reduced values, and a significant difference in diameter persisted between the two groups.